Generation and trapping of chiral enolates

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Abstract

Chapter one is an introduction to the aldol reaction. A discussion of the recent catalytic and asymmetric developments of this reaction is also included. In addition, the process of soft enolisation is presented and exemplified with several aldol additions. The project of soft enolisation to generate *in situ* chiral metal enolates, their trapping by aldehydes and a post aldol addition cyclisation with an isothiocyanate substituent is also presented.

Chapter two describes the synthetic work carried out. The first part describes the discovery and the optimisation of a catalyst for the soft enolisation and racemic aldol reaction using commercially available starting materials. This reaction is then successfully applied to a range of aromatic aldehydes. The second part reveals the improvement towards the asymmetric catalytic aldol reaction by employing various chiral ligands. The synthesis and use of a bidentate substrate for this asymmetric aldol reaction is also reported. Finally, the initial results of the extension of this research to other electrophiles are presented.

Chapter three provides detailed experimental procedures.

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Abbreviations

Ac	Acetyl
App.	Apparent
Ar	Aryl
Benz	Benzene
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
BOx	Bisoxazoline
c	Cyclo
CI	Chemical Ionisation
Cp	Cyclopentadiene
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	(Diethylamino)sulphur trifluoride
DBF	Dibenzofuran
DBU	1,8-Diazabicyclo[5.4.0]]undec-7-ene
DCM	Dichloromethane
de	Diastereomeric excess
DIPEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
ee	Enantiomeric excess
EI	Electron Impact
er	Enantiomeric ratio
ES	Electrospray
Eq.	Equation

equiv.	Equivalent
Et	Ethyl
FAB	Fast Atom Bombardment
g	Gram
h	Hour
HPLC	High Pressure Liquid Chromatography
i	Iso
ind	Indane
IR	Infrared
J	coupling constant
L	Ligand or Litre
LDA	Lithium Diisopropyl Amide
m	Multiplet
m	*meta*
Me	Methyl
mg	milligram
min	Minute
mL	millilitre
mp	Melting point
MS	Molecular sieves
^{n}Bu	*normal*-Butyl
NCS	Isothiocyanato
NEP	*N*-Ethylpiperidine
NMIm	*N*-Methylimidazole
NMM	*N*-Methylmorpholine

NMR	Nuclear Magnetic Resonance
o	*ortho*
ON	Overnight
Ox	Oxazoline
p	*para*
Ph	Phenyl
ppm	Part per million
Py	Pyridine
q	quartet
RT	Room temperature
s	*Sec*
sat.	Saturated
t	Triplet
TBAHS	Tetrabutylammonium hydrogen sulphate
^{t}Bu	*tert*-Butyl
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMDEA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	Tolyl
tr	Retention time
Y	Yield
*L	Chiral ligand

Stereochemical notation

Throughout this thesis, the graphical representation of stereochemistry follows the conventions proposed by Maehr.[i]

Thus, solid and broken wedges as in **A** denote absolute configuration of the chiral element. Narrowing both the solid and the broken wedges indicate increasing distances from the viewer. Solid and broken bold lines as in **B** represent the relative configuration and specifically denote racemic character.

A **B**

[i] Maehr, J. *J. Chem. Educ.* **1985**, *62*, 114-120.

Contents

I Introduction

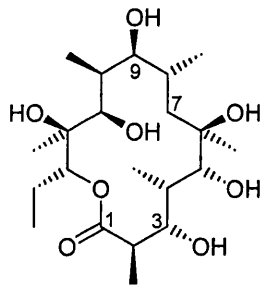
The work presented herein develops a new methodology for the generation and trapping of chiral enolates, initially by working on the aldol reaction. Myriads of natural products include a β-hydroxy carbonyl moiety; functionality produced by the aldol reaction. Recent examples of such products are illustrated bellow. They demonstrate the need for good synthetic techniques to control the synthesis of this important functionality. The basis of the aldol reaction and its stereochemical outcome are briefly exposed, followed by a discussion of the Mukaiyama aldol reaction. The catalytic version of this reaction is presented from its origins as well as new discoveries. Then follows a discussion of the use of a few biocatalysts such as antibodies and small molecules, inspired by natural aldolases. This leads to the development of more versatile direct catalysts for the aldol reaction, mainly bimetallic species. Finally, the concept of soft enolisation is discussed and introduces the proposal of the work carried out towards the asymmetric catalytic aldol reaction. This is not intended to present a comprehensive review of the aldol reaction, rather to highlight important features of the process relevant to the discussion presented in the results and discussion section.

I 1 β-Hydroxy carbonyl units in natural products

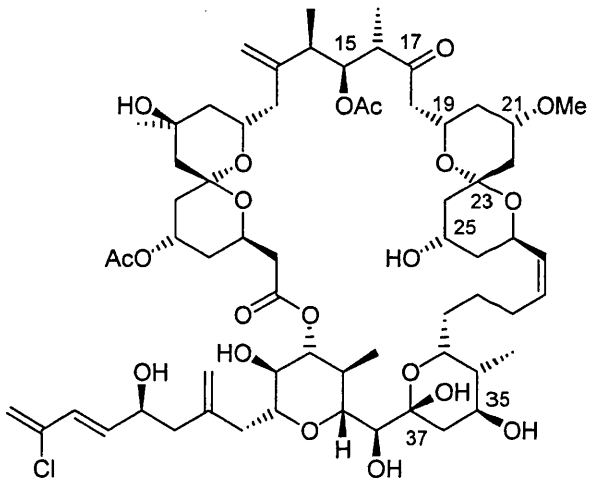
I 1A Recent examples in natural product synthesis

Many natural products are imbedded with a β-hydroxy carbonyl unit or involve this important unit in their synthesis. This functionality can be obtained by the aldol reaction as recently reported by Woerpel *et al.* in the stereocontrolled synthesis of (9*S*)-dihydroerythronolide A **1** (Figure 1).[1]

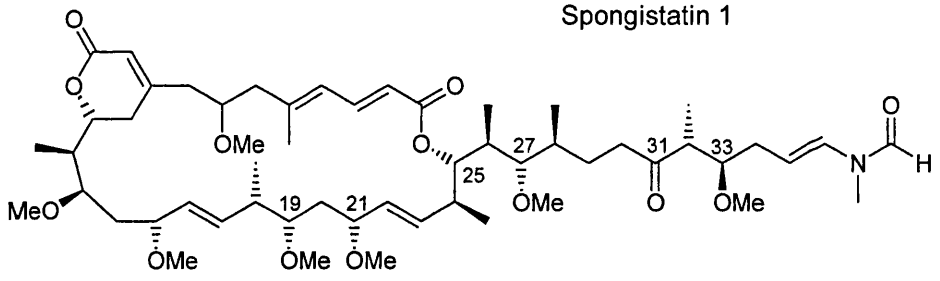
Figure 1. Examples of natural products including β-hydroxy carbonyl structure.



1
(9*S*)-Dihydroerythronolide A



3
Spongistatin 1



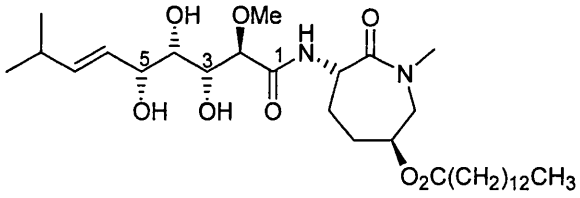
2
Reidispongiolide A

The β-hydroxy carbonyl functionality at [C1-C3] was introduced using a titanium tetrachloride mediated aldol reaction. The stereochemical outcome was controlled by the combined actions of a chiral ligand on the Lewis acid and a chiral auxiliary. A second aldol reaction mediated by tin triflate was required to connect stereoselectively the two final fragments of the molecule [C7-C9]. The carbonyl moiety was then reduced leaving the hydroxy function unchanged. A second example of a natural product that includes a β-hydroxy carbonyl unit is reidispongiolide A **2** and is situated at [C31-C33] (Figure 1). This new actin-binding cytotoxic macrolactone retains activity toward multidrug resistant cancer cell lines. Partial synthesis of **2** has been reported by Paterson *et al.*[2] Two more β-hydroxy carbonyl units were formed and then reduced to obtain 1,3-diol functionality [C19-C21] and [C25-C27]. These aldol reactions utilised boron enolates with substrate or ligand control of the stereochemistry. A final example of a natural product including the β-hydroxy carbonyl unit is spongistatin 1 **3** (Figure 1).[3,4,5] This bis-spiroketal macrolide has gained considerable attention due to its potent growth inhibitory activity against a wide range of drug resistant cancer cell lines. Several groups have reported the synthesis of **3** or analogues, which helped to confirm the relative and absolute stereochemistry. In Paterson's syntons, the β-hydroxy carbonyl unit [C15-C17] was introduced *via* a boron mediated aldol reaction. Then, the β-dihydroxy units [C19-C21], [C23-C25] and [C33-C35] were accessed using a boron mediated aldol reaction. In the case of [C23-C25] a triple asymmetric induction was observed.

I 1B α,β-Dihydroxy carbonyl template

In addition to the β-hydroxy carbonyl unit obtained by the aldol reaction, α-hydroxy substituted starting materials can provide access to α,β-dihydroxy carbonyl units. A recent example has been reported by Boeckman Jr. *et al.* in the enantioselective total synthesis of bengamide B **4** (Figure 2).[6,7] The natural product shows potentially useful anti-proliferation activity and could be indicated as a therapeutic for drug resistant solid tumours. The side chain last connected to the caprolactam was obtained by two subsequent aldol reactions using α-etherate substituted starting materials. The first α,β-dihydroxy carbonyl unit [C3-C5] was introduced using a boron enolate and the stereochemistry was controlled by a chiral auxiliary. The second α,β-dihydroxy carbonyl unit [C1-C3] was obtained by the Lewis acid mediated addition of a phenylthioketene acetal to the previously formed α,β-dihydroxy carbonyl molecule.

Figure 2. Structure of bengamide B.



4

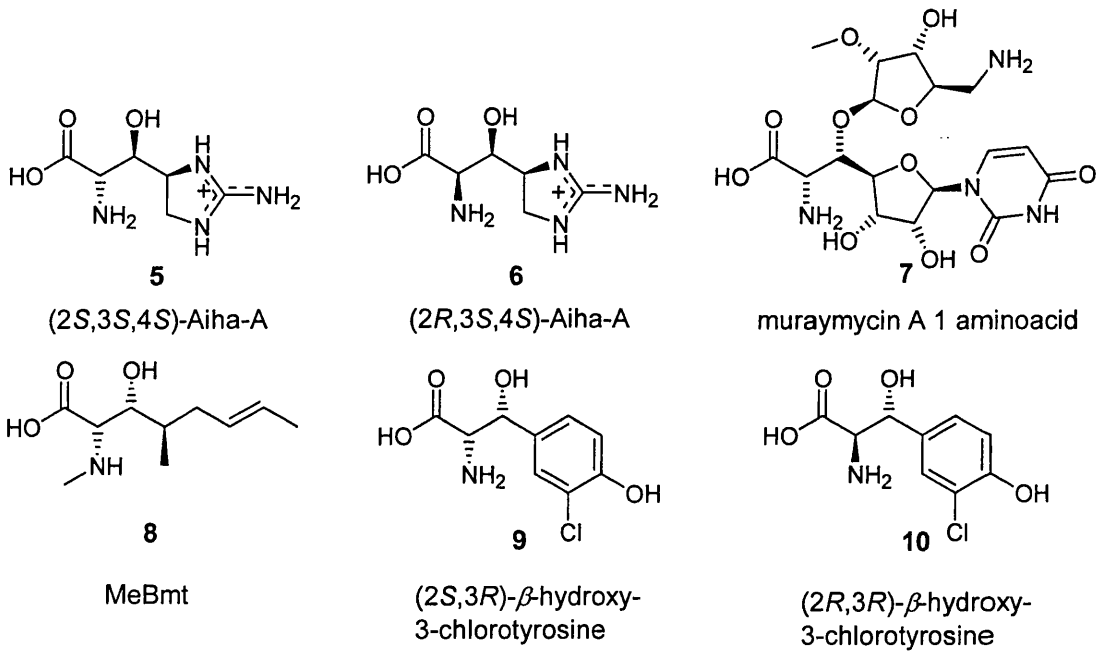
Bengamide B

I 1C α-Amino-β-hydroxy carbonyl unit

A third class of interesting functionality is the α-amino-β-hydroxy carbonyl unit included in many naturally occurring molecules. The first example is the α-amino-β-hydroxy acids of mannopeptimycins. These molecules are antibacterial glycopeptides

initially isolated in the late 1950s and produced as a mixture by a strain of *Streptomyces hygroscopicus*.[8] He *et al.* reported the structural characterisation of these products. The two interesting α-amino-β-hydroxy acids are the diastereomers (2*S*,3*S*,4'*S*)- and (2*R*,3*S*,4'*S*)-α-amino-β-[4'-(2'-iminoimidazolidinyl)]-β-hydroxypropionic acid (Aiha-A **5** and Aiha-B **6** respectively) (Figure 3).

Figure 3. Examples of β-hydroxy-α-amino acids.



A second example of an interesting naturally occurring α-amino-β-hydroxy acid was reported by McDonald *et al.*[9] Nineteen muraymycins (cell-wall biosynthesis inhibitors) were isolated and their structures established. An unusual feature of these molecules is the dioxodihydropyrimidyl-dihydroxy-tetrahydrofuran moiety on the amino acid **7** (Figure 3). Only the relative stereochemistry of this cyclic guanidine amino acid residue could be assigned (2*S**,3*S**). The total synthesis of this molecule will confirm the absolute stereochemistry of the terminal amino acid. Another interesting β-hydroxy-α-amino acid is (4*R*)-4-((*E*)-2-butenyl)-4,*N*-dimethyl-L-threonine **8**, which is an unusual

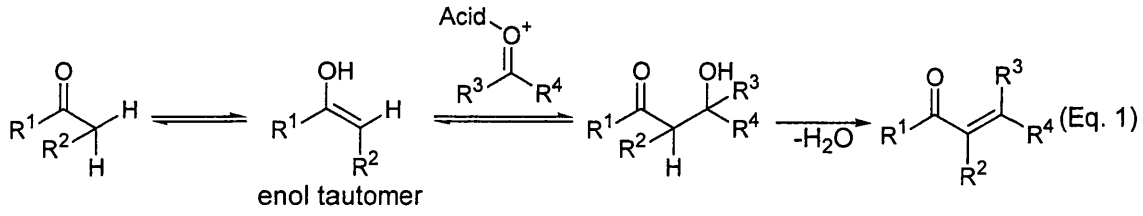
C_9 amino acid (MeBmt) (Figure 3). As part of the immunosuppressive peptide cyclosporine, MeBmt appeared to be critically involved in the biological activity of the chemotherapeutic agent. The need for a synthetic route to MeBmt and analogues was then required and developed by Evans *et al.* using a tin mediated aldol reaction.[10] The *syn*-aldol adducts were obtained with a high level of diastereoselectivity. A final example of a β-hydroxy-α-amino carbonyl is that of *syn*- and *anti*-β-hydroxy-3-chlorotyrosine **9** and **10**, a subunit of the glycopeptide vancomycin (Figure 3).[11] The total synthesis of these molecules and analogues attracted the work of many groups. These amino acids and analogues have been synthesised by the aldol reaction in some cases.[12] These few examples illustrate how β-hydroxy carbonyl unit features in numerous natural products and their synthesis has become important. The aldol reaction is an excellent methodology for this purpose and gives access to this moiety and has been used for more than a century. In the next section, the background of this reaction will be briefly exposed.

I 2 Aldol reaction Background[13]

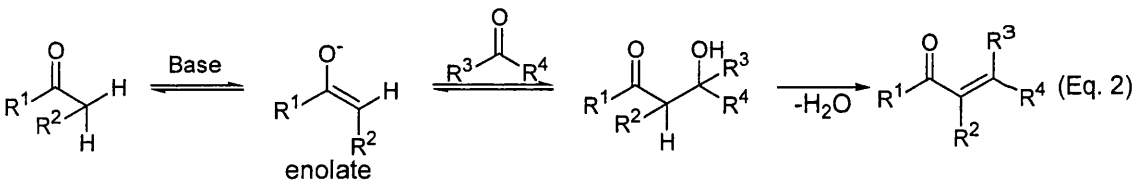
I 2A Acid/base catalysis

The aldol reaction is an important reaction for organic synthesis since it allows the formation of a new carbon-carbon bond and possibly two new stereogenic centres. Acid or base catalysed dimmer construction from aldehydes or ketones were first discovered and reported more than a century ago. The reaction occurs between the nucleophilic carbon in the α-position to a carbonyl and the carbon of an electrophilic carbonyl moiety. The acid-catalysed reaction proceeds *via* the enol tautomer of a

nucleophile which then reacts with an acid activated electrophilic carbonyl (Eq. 1). The product obtained is a β-hydroxy aldehyde or ketone. The retro reaction is also feasible, regenerating starting materials. In addition, the product could undergo a further dehydration, forming an α,β-conjugated carbonyl.



The more common base-catalysed reaction proceeds *via* the formation of an enolate (Eq. 2). A base abstracts a proton on the α-carbon to the carbonyl of the nucleophile. This activated nucleophile then attacks the electrophilic carbonyl to form the aldol adducts. Like the acid catalysed process, this reaction is reversible. Moreover, if a second enolisation is possible then it might lead to elimination of water to form an enone or an enal.

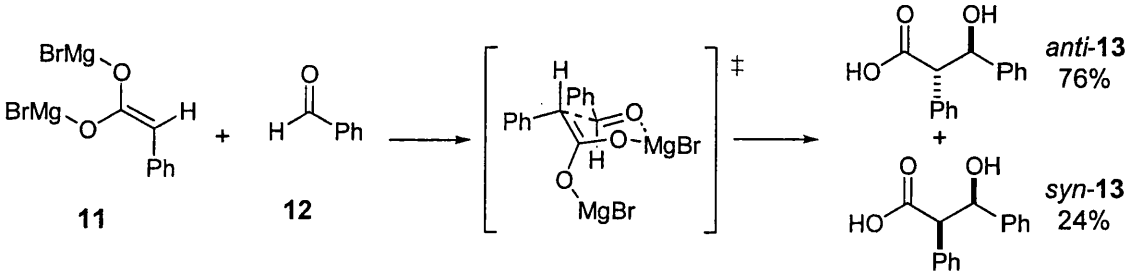


However, the outcome of the reaction is usually a mixture of different products and starting materials, depending on the substituents R^1-R^4. Indeed, several regioisomers, diastereomers and enantiomers can be synthesised. Therefore, many attempts have been launched to favour the formation of one product selectively and to rationalise the stereochemistry observed.

I 2B Stereochemistry

To become synthetically useful, the stereochemistry of the products of the aldol reaction needs to be predictable. One of the first attempts to account for this stereochemistry came from Zimmerman and Traxler.[14] They observed in their work on the Ivanov reaction of the preformed magnesium dianion of phenylacetic acid **11** with benzaldehyde **12**, that the diastereomer *anti*-**13** was favoured over the *syn*-**13** (*syn*:*anti* = 24:76) (Scheme 1). They consequently proposed that the reaction proceeded through the cyclic transition state depicted in Scheme 1. One of the two magnesium cations was chelated by both the oxygen of the aldehyde and one of the oxygen atoms of the carboxylate. In order to minimise the steric interactions, the two phenyl-substituents were preferentially occupying the equatorial positions on the six membered cycle, forming preferentially *anti*-**13**.

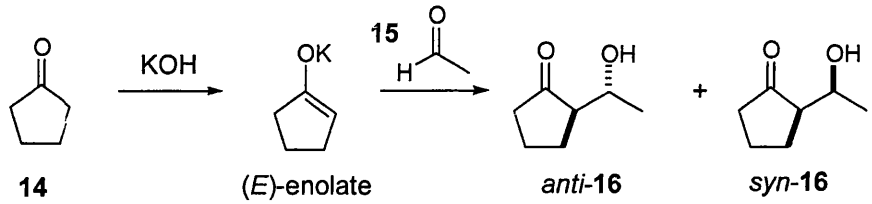
Scheme 1. Stereochemistry of the Ivanov reaction.



Later, Dubois and co-workers highlighted the kinetic and thermodynamic control of the aldol reaction.[15,16] They studied the effects of the solvent and the temperature on the equilibrium of the products *syn*-**16** and *anti*-**16** (Scheme 2). They noticed that the (*E*)-enolate obtained from cyclopentanone **14** treated with methanolic KOH, reacted with acetaldehyde **15** to give preferentially the *syn*-**16** diastereomer under the

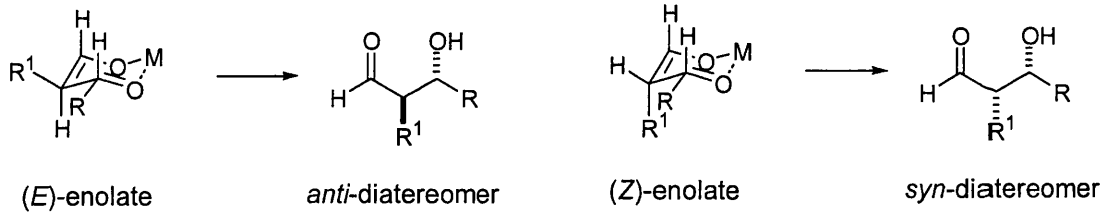
thermodynamic conditions (4 hours at 5 °C). However, under kinetic conditions (15 seconds at -20 °C) the (*E*)-enolate gave preferentially the opposite diastereomer *anti*-**16**.

Scheme 2. Kinetic and thermodynamic control of the aldol reaction.



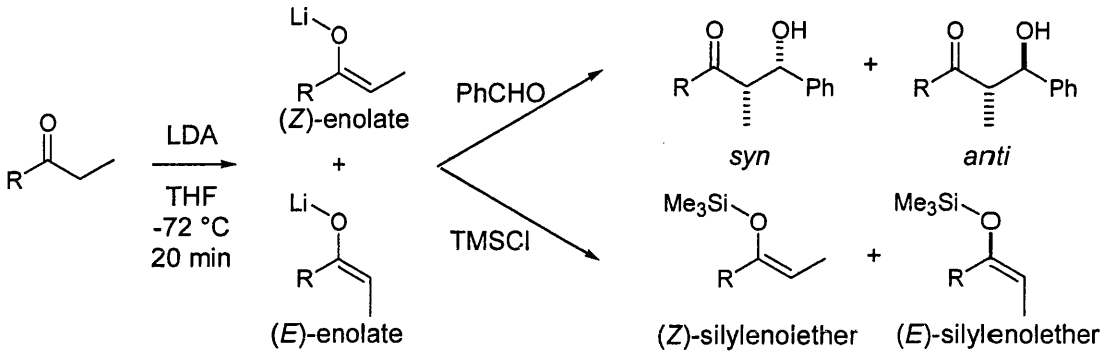
These two previous reports set the basis for the fundamental mechanistic concepts of the aldol reaction under kinetic control (Scheme 3). Usually, the aldol reaction proceeds through a cyclic chair-like transition state built around a metal centre. In analogy to cyclohexane, the largest substituent of the electrophile adopts the equatorial position to minimise steric interactions.[17] Consequently, an (*E*)-enolate would normally give access to an *anti*-diastereomer whereas a (*Z*)-enolate would give access to a *syn*-diastereomer.

Scheme 3. Chair-like transition state with (*E*)- and (*Z*)-enolates.



More recently, Heathcock *et al.* studied the diastereoselectivity of the aldol reaction.[18] The survey correlated the ratio of *syn*- and *anti*-diastereomer obtained by the reaction of preformed lithium enolates with benzaldehyde **12** to the ratio of starting enolate (Table 1).

Table 1. Correlation between *Z*:*E* and *syn*:*anti*.



Entry	R	*Z*:*E*	*syn*:*anti*
1	^{t}Bu	>98:2	> 98:2
2	Mesityl	5:95	8:92
3	CH_3O	5:95	62:38

The latter ratio was determined by trapping the enolate mixture with chlorotrimethylsilane (TMSCl). Complete kinetic stereoselection was observed for bulky R substituents. Indeed entries 1 and 2 showed a good correlation between the enolate geometry and the stereochemistry of the aldol product. The (*Z*)-enolate gave the *syn*-aldol product (Entry 1) while the (*E*)-enolate gave the *anti*-aldol product preferentially (Entry 2). However, for ketones or esters with smaller substituents like the methyl ester of entry 3, the stereoselectivity decreased or disappeared. Many examples of aldol reactions support the concept of chair-like transition states but the stereochemistry of the reacting enolate and of the aldehyde might impair the diastereomeric ratio. In addition, the presence of other coordinating sites and the nature of Lewis acid will change the transition state for a different closed transition state or even for an open one. The geometry of the enolate intermediate has a considerable effect on the selectivity of the reaction and its formation must be controlled as much as possible. Small R substituents generally form (*E*)-enolates whereas increasing its size increases the amount of (*Z*)-enolates. However, a bulky base gives more of the (*E*)-enolates. To shortcut the problem of enolate stereochemistry, Mukaiyama ingenuously

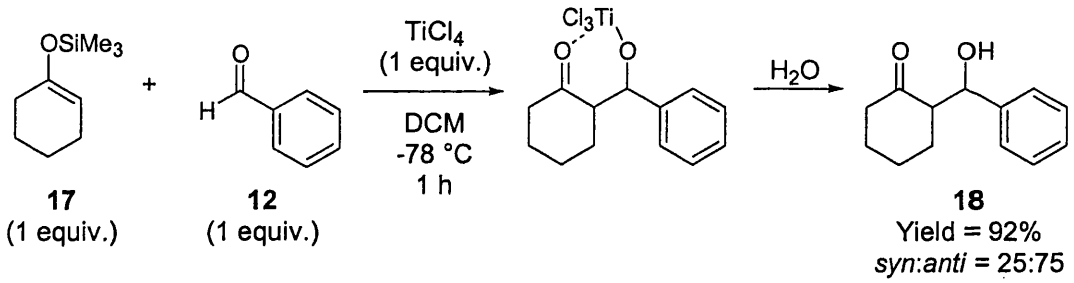
reported the use of silyl enol ethers as latent enolates. Their fixed stereochemistry has given excellent results and is presented in the following section.

I 3 Mukaiyama aldol reaction

I 3A Original research

Thirty years ago, Mukaiyama *et al.* reported the nucleophilic addition of latent enolates such as enol silanes to aldehydes or ketones activated by a Lewis acid. This was a seminal study in the domain of the aldol reaction.[19] They discovered that titanium tetrachloride promoted the reaction of 1-trimethylsilyloxycyclohex-1-ene **17** with benzaldehyde **12**, to yield after 1 hour at -78 °C in dichloromethane and subsequent hydrolysis, the aldol product 2-(1'-hydroxybenzyl)-cyclohexan-1-one **18** (92%) with good diastereoselectivity (*syn*:*anti* = 25:75) (Scheme 4).

Scheme 4. Mukaiyama aldol reaction.



They found that $TiCl_4$ was a better Lewis acid than boron trifluoride etherate and tin tetrachloride in term of yields. Their best results were obtained with one equivalent of Lewis acid; even so, they obtained the aldol products in 80% yield with only 13 mol% of $TiCl_4$. They also extended the reaction to other aldehydes (Table 2).

Table 2. Scope of the Mukaiyama aldol reaction with **17**.

Entry	Electrophile	T (°C)	Yield (%)	*syn*:*anti*
1	**12**	-78	92	25:75
2	$(CH_3)_2CHCHO$	-78	92	50:50
3	$(C_6H_5CH_2)_2CO$	25	64	-

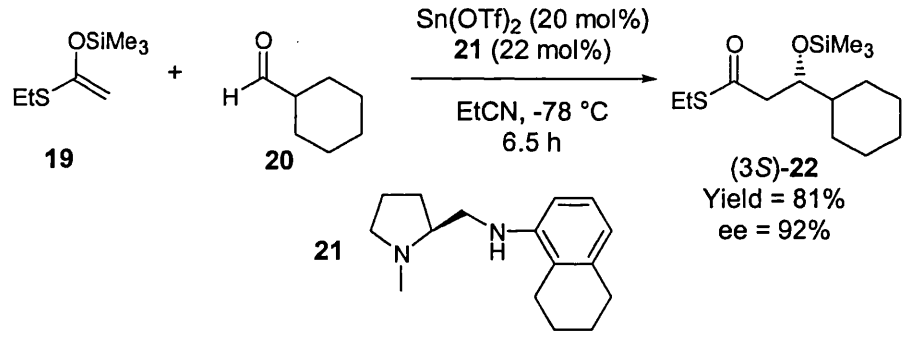
For entries 1 and 2, the adducts were obtained in good yields at -78 °C. However, the stereoselectivity of the reaction was unreliable and gave an equal mixture of *syn*- and *anti*-aldol products in entry 2. Regarding the addition to ketone electrophiles, the temperature had to be increased to room temperature to give reasonable yields (Entry 3). They also applied the reaction to silyl enol ethers prepared from aldehydes but the products proved to be unstable and to dehydrate on silica.

I 3B Catalytic asymmetric Mukaiyama aldol reaction[20,21]

Starting from the basis detailed above, several groups have been working on the Mukaiyama aldol reaction and evolved it to a catalytic asymmetric reaction. Here are presented Mukaiyama's own improvement and the contributions of the Masamune, Evans and Carreira groups. A major problem encountered during the development of stereo-controlled versions of the Mukaiyama aldol reaction was the release of TMSCl as a side product in the reaction media. This silicon-containing molecule was able to catalyse the reaction, potentially generating racemic products.[22] However, Mukaiyama, Kobayashi and co-workers developed a powerful system for the reaction of silyl ketene acetals of thioesters with aldehydes.[23,24] They obtained excellent diastereo- and enantioselectivities using chiral diamines coordinated to Sn(II) triflate and tributyltin fluoride (Bu_3SnF).[25,26] In the absence of Bu_3SnF the products were obtained as

racemates, which suggested that a stoichiometric amount of this additive was suppressing the competing trimethylsilyl triflate catalysed reaction.[27] They then improved this reaction to a catalytic asymmetric version and obtained good results too (Scheme 5).[28] The catalyst was prepared prior to use, by mixing a solution of $Sn(OTf)_2$ in propionitrile and a solution of chiral diamine ligand **21** in propionitrile. The temperature was lowered to -78 °C and a mixture of the silyl ketene acetal of *S*-ethyl ethanethioate **19** and cyclohexylcarboxaldehyde **20** was added over 4.5 hours. The adduct (3*S*)-**22** was then isolated in 81% yield and 92% ee.

Scheme 5. Catalytic asymmetric Mukaiyama aldol reaction.

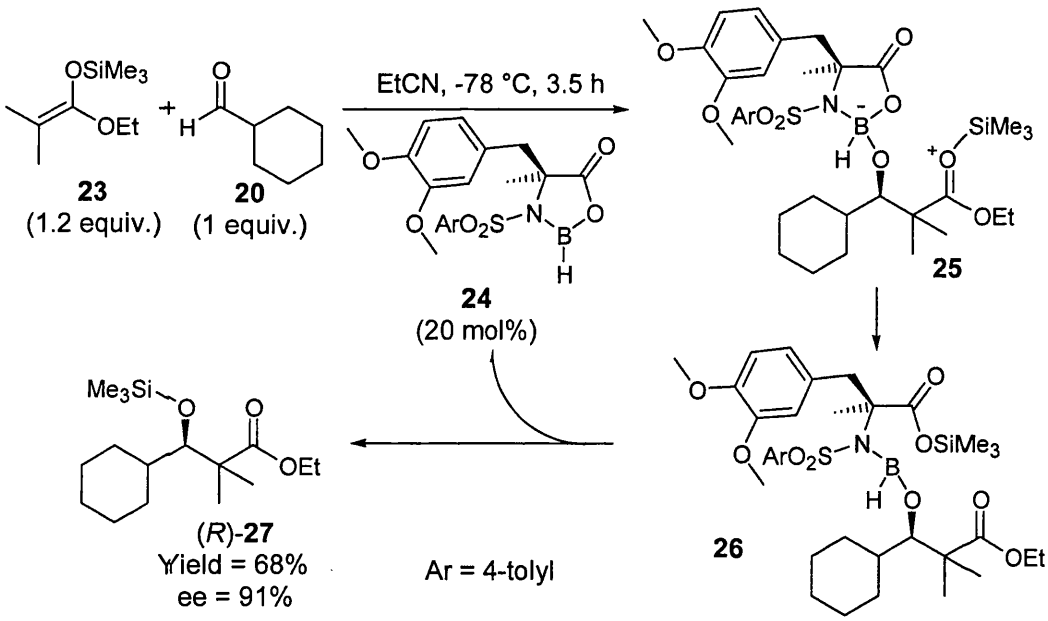


The process was applied to a range of aldehydes giving good yields and ee. This successful result was attributed to the coordination of the metal centre by the solvent, increasing the electron density around the tin alkoxide. The reactivity of this metal alkoxide towards silylation was therefore accelerated. The TMSOTf was trapped faster, regenerating the active catalyst, increasing its turnover and the stereoselectivity of the reaction.

In the meantime, Masamune *et al.* had developed a different catalyst for the activation of the electrophile of the Mukaiyama aldol reaction.[29,30] Concerned by possible catalysis from silicon species released in the reaction media, they elaborated a

catalyst that could be silylated on the ligand and thus accelerate the silylation of metal alkoxide thereby regenerating the active catalyst. A slow addition over 3.5 hours of aldehyde **20** to a solution of silyl ketene acetal **23** (1.2 equiv.) and the chiral Lewis acid **24** (20 mol%) in propionitrile at -78 °C was proposed to form the intermediate **25**. The silylation of the ligand would form the monodentate boron molecule **26** that would cyclise and transfer the silicon onto the alkoxide, regenerating the catalyst **24** and producing the silylated aldol product (*R*)-**27** in 68% yield and 91% ee (Scheme 6). They suggested that the slow addition of aldehyde would reduce the number of monodentate species **26** that might also catalyse the reaction but with less stereoselectivity. This reaction was successfully applied to other aldol or silyl enol ethers giving good yields, excellent diastereoselectivity and ee's up to 99%.

Scheme 6. Asymmetric Mukaiyama aldol reaction catalysed by a borane.

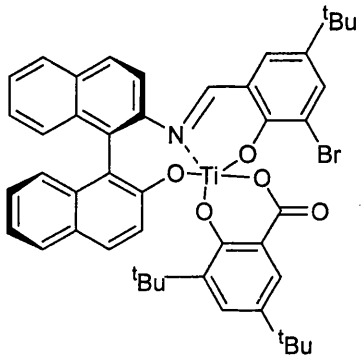


Carreira and co-workers have utilised a related mechanism of intramolecular shuttle of the trimethylsilyl moiety using the Ti(IV) complex **28** (Scheme 7). This

catalyst was general in its scope and gave excellent yields for aliphatic and aromatic aldehydes reacting with silyl enol ethers or silyl dienolates. Reactions conducted at -10 °C in ether with as little as 0.5 mol% of catalyst gave good yields (72-99%) and high levels of asymmetric induction (88-99% ee's).[31,32,33]

Scheme 7. Carreira's Ti(IV) catalyst for aldol addition reaction.

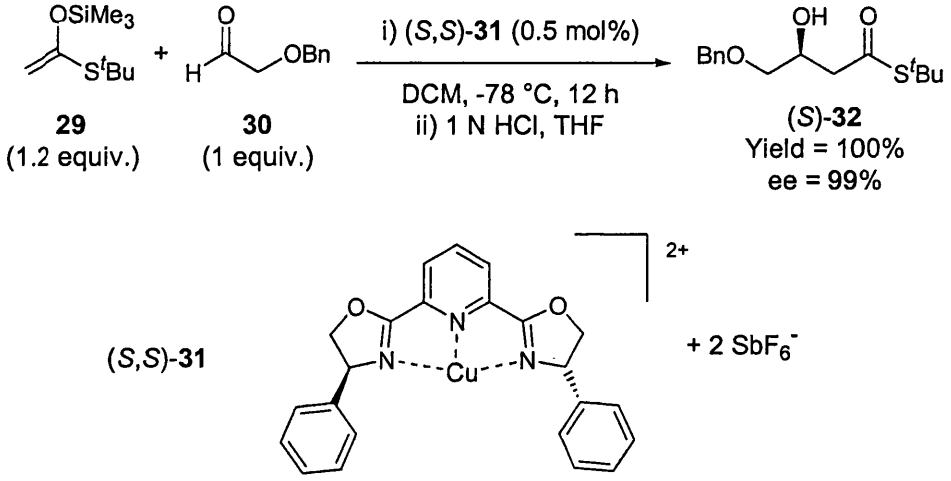
28



A few years later, Evans *et al.* reported efficient *syn*-selective Mukaiyama aldol reactions.[34,35] One of their powerful catalysts used was the tridentate bis(oxazolinyl)pyridine (PyBOx) copper(II) hexafluoroantimonate (*S*,*S*)-**31** (Scheme 8).[36] As little as 0.5 mol% of this catalyst was sufficient to bring to completion the addition of the silyl ketene acetal **29** (1.2 equiv.) to benzyloxyacetaldehyde **30** (1 equiv.). After 12 hours at -78 °C, in DCM and desilylation in THF by 1N HCl, the aldol product **32** was obtained in *ca.* 100% yield and 99 % ee. This reaction was found to be quite general with respect to the silyl ketene acetal structure but the requirement for a chelating substituent on the aldehyde was critical to catalyst selectivity. Indeed, bulkier ether aldehydes gave lower ee and non-chelating aldehydes led to racemates. In addition, the use of α-substituted silyl ketene acetals afforded preferentially the *syn*-aldol, regardless of the geometry of the nucleophile (diastereoselectivity ranging from 95:5 to 97:3 with ee's > 95%). This was rationalised by the attack of the silyl ketene

acetal *via* an open transition state on the *si* face of the chelated aldehyde minimising the number of repulsive gauche interactions.

Scheme 8. Cu(II) catalysed enantioselective Mukaiyama aldol reaction.



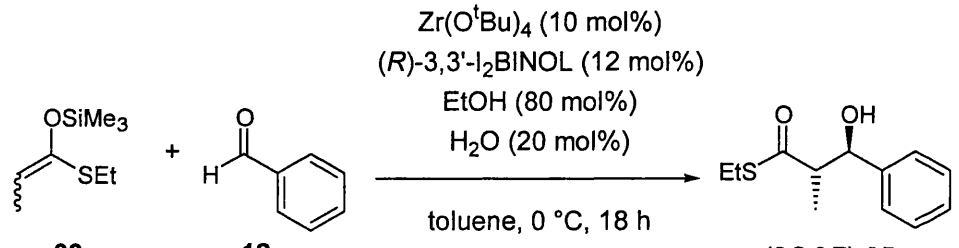
The process was extended to glyoxylate and pyruvate esters giving excellent regioselectivity, good yields (around 90%) and excellent enantioselectivity (> 92%).[37,38] Changing copper triflate for tin triflate allowed the selective formation of the opposite diastereomers.

I 3C Recent advances in the Mukaiyama aldol reaction

Except for the last substrates mentioned most of the developed diastereoselective Mukaiyama aldol reactions generated *syn*-adducts. On the contrary, Kobayashi and co-workers, recently detailed a highly *anti*-selective catalytic Mukaiyama aldol reaction promoted by a zirconium Lewis acid (Table 3).[39,40] Initially, they developed an effective enantioselective catalytic system, furnishing aldol adducts in good yield and enantioselectivity. Their catalyst was formed by the association of

zirconium tetra-*tert*-butoxide ($Zr(O^tBu)_4$), (*R*)-3,3'-diiodo-1,1'-binaphthalene-2,2'-diol ((*R*)-3,3'-I_2BINOL) and a primary alcohol as a proton source to help the regeneration of the catalyst. In addition, they later discovered that the addition of a small amount of water was increasing the activity of the catalyst and was improving the reproducibility of the experiments. From their NMR experiments, they assumed that the water was taking part in the formation of the complex **34**, the active catalytic species of the reaction. With this catalyst, they also obtained *anti*-diastereomer selectively, regardless of the geometry of the starting silyl ketene acetals (Entries 1-2). Reactions of mixtures enriched in one of the (*E*)- or (*Z*)-silyl ketene acetals **33** (1.2 equiv.) with benzaldehyde **12** (1 equiv.), catalysed by **34** furnished the aldol adduct (2*S*,3*R*)-**35**. Yields were above 63%, and the diastereoselectivity was about (8:92) in favour of the *anti*-diastereomer with ee greater than 95%.

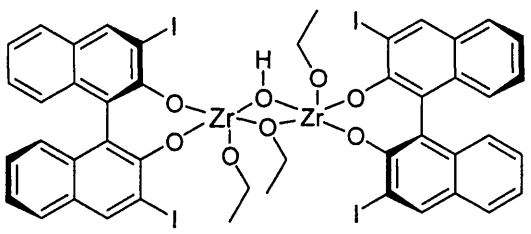
Table 3. *Anti*-selective Zr catalyst for the Mukaiyama aldol reaction.



33 (1.2 equiv.) **12** (1 equiv.) (2*S*,3*R*)-**35**

Entry	**33** *E*/*Z* ratio	Yield (%)	*syn*-*anti*	(2*S*,3*R*)-**35** ee (%)
1	88/12	63	9/91	95
2	7/93	77	7/93	98

Assumed catalyst : **34**



The catalytic cycle was proposed to proceed through the activation of the aldehyde by the Lewis acid. *Anti*-selectivity was ascribed to steric repulsions between the α-alkyl substituent of the nucleophile and the Lewis acid in an open transition state. After carbon-carbon bond formation, the ligand was silylated on the oxygen. The primary alcohol trapped the trimethyl silyl species, regenerating the active catalyst and furnishing the β-hydroxy carbonyl. Many other variations of the Mukaiyama aldol reaction have been developed and recently, the focus has been put on the asymmetric catalytic Mukaiyama aldol reaction mediated by rare earth metals in aqueous media.[41]

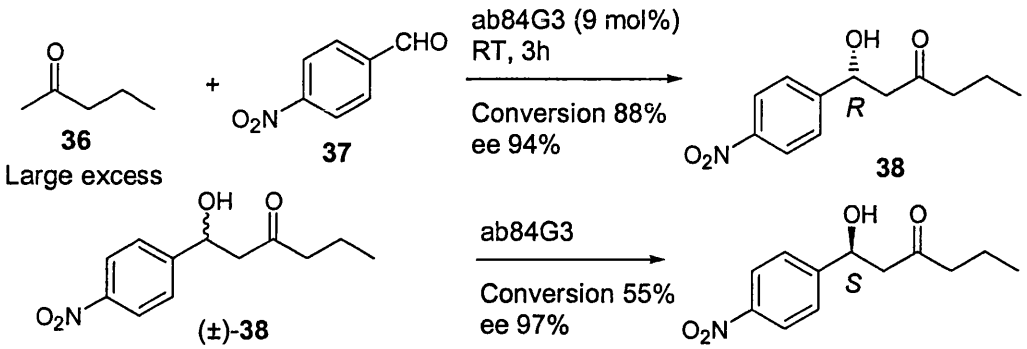
I 4 Biocatalysts

I 4A Aldolase antibodies

One of the drawbacks of the Mukaiyama aldol reaction is the need for preformed silyl enol ethers. Biocatalysts such as aldolases, catalytic antibodies and small enzyme mimetics have been intensively studied by several groups and provide direct routes for aldol reaction between two unmodified carbonyl compounds. Class I aldolases catalyse the reversible reaction through a Schiff base intermediate between an active site lysine and the carbonyl of the substrate.[42] Class II aldolases require a zinc cofactor acting as a Lewis acid to mediate the reaction.[43] The groups of Barbas and Lerner have developed a series of aldolases mimics.[44] These antibodies use the enamine mechanism of naturally occurring Class I aldolases. Recently, the group of Governeur *et al.* reported the use of the antibody 84G3 (ab84G3) in an effective asymmetric catalysis for the regioselective and enantioselective formation of β-hydroxy carbonyl moieties (Scheme 9).[45] The addition of pentan-2-one **36** to 4-nitrobenzaldehyde **37** was accomplished at room

temperature in three hours by ab84G3 to give the aldol product (*R*)-**38** in 88% conversion and 94 % enantiomeric excess. No regioisomer was observed.

Scheme 9. Asymmetric catalysis by ab84G3.



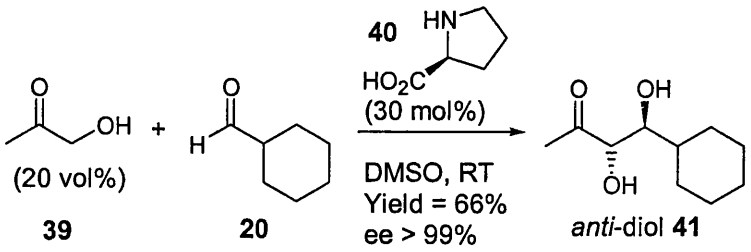
The enolisation occurred only at the primary α-carbon centre. The other enantiomer (*S*)-**38** could be obtained by retro-aldol reaction of a racemic mixture of **38**. The kinetic resolution was stopped after conversion of 55 % of the racemic mixture. The reaction was quenched to give (*S*)-**38** in 97% ee. This methodology was also efficient for a range of substrates but a large excess of ketone was required to favour the aldol addition. Moreover, these catalytic antibodies needed to be selected through reactive immunisation to transition state analogues which was a time consuming process.

I 4B List's proline catalyst

Recently, much smaller molecules than catalytic antibodies and aldolases were used in the asymmetric catalysis of the aldol reaction.[46,47] List *et al.* extended the Hajos-Parrish-Eder-Sauer-Wiechert reaction to the aldol reaction,[48,49] a system based on the amino acid L-proline **40** (Scheme 10).[50,51,52] The addition of hydroxyacetone **39** to cyclohexylcarboxaldehyde **20** was catalysed by L-proline **40** (30 mol%) in DMSO at

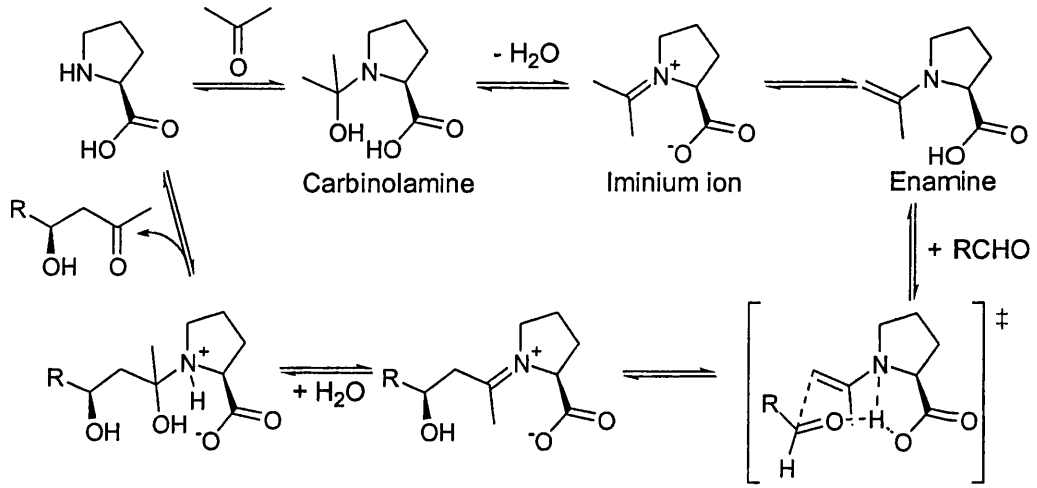
RT. The anti-diol adduct **41** was obtained in 60% yield with a regioselectivity > 20:1, a diastereoselectivity > 20:1 and an enantioselectivity > 100:1.

Scheme 10. Proline catalysed aldol reaction.



Various other aldehydes were tested and gave good yields and excellent stereoselectivity. The reaction had the advantages of being direct, water tolerant and conducted at RT. The enantioselectivity was explained by an enamine mechanism, *i.e.* a metal free Zimmerman-Traxler cyclic transition state (Scheme 11).

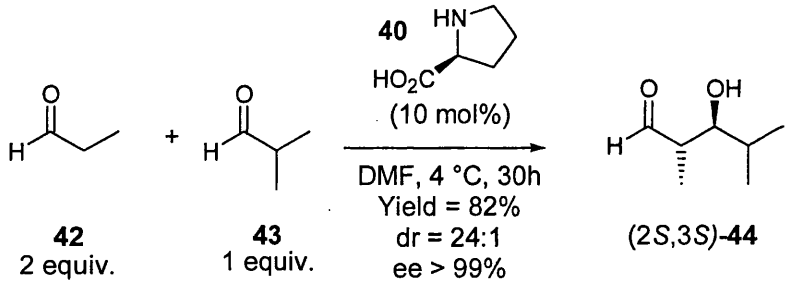
Scheme 11. List's proposed enamine mechanism with acetone.



The proline amine **40** attacked and activated the donor substrate carbonyl. After dehydration to an iminium ion and rearrangement, the enamine nucleophile formed a

tricyclic hydrogen bonded chair-like transition state with the acceptor carbonyl. Addition of a molecule of water and expulsion of the aldol product regenerated the proline catalyst **40**. This proline catalysed reaction mimics the Class I aldolase reactions. However, as for the catalytic antibody catalysed aldol reactions, the need for an excess of one of the substrates makes this method rather cumbersome. Nevertheless, MacMillan *et al.* have recently reported the use of proline as a catalyst for the direct aldehyde cross aldol reaction.[53] In contrast to the proline mediated ketone addition, a small catalyst loading of 10 mol% and shorter reaction times were sufficient. Their best results were observed using *N,N*-dimethylformamide as solvent. The addition of propionaldehyde **42** (2 equiv.) to isobutyraldehyde **43** (1 equiv.) at 4 °C for 30 hours afforded (2*S*,3*S*)-3-hydroxy-2,4-dimethylpentanal **44** in 82% yield, in 24:1 *anti*-diastereoselectivity and in ee > 99% (Scheme 12).

Scheme 12. MacMillan's enantioselective direct aldehyde cross aldol reaction.



Other groups have reported the use of different small molecules as catalysts for the direct aldol reaction. Nornicotine, a nicotine-related alkaloid found in tobacco and *in vivo* as a minor metabolite of nicotine, was reported as an active catalyst for the aldol addition in aqueous phosphate buffers.[54] Janda *et al.* were able to isolate the enamine intermediate formed with acetone and proposed a Class I aldolase mechanism. Finally, the use of proline or amino acids in conjunction with a Lewis acid co-catalyst such as

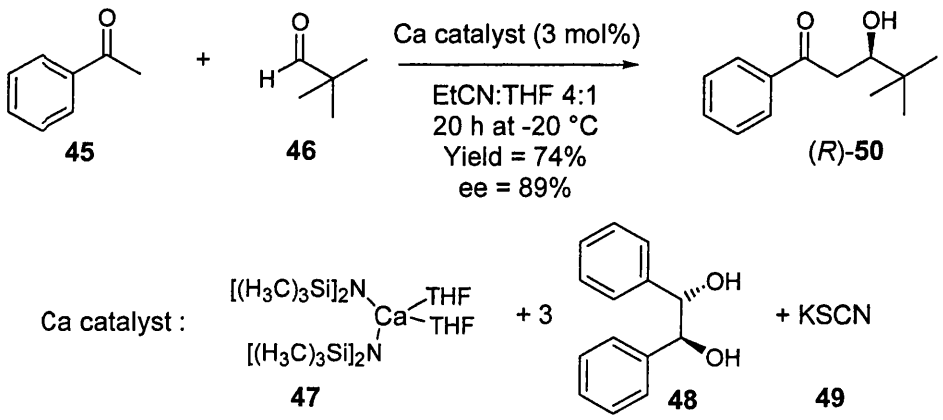
zinc II was explored.[55,56] The yields of these reactions were excellent but the enantiomeric excesses remained low (24-56%), probably due to the presence of different simultaneous catalysts.

I 5 New developments

I 5A Noyori's calcium II catalyst

In addition to the former biocatalysts, several metallic complexes have recently been developed as catalysts for the direct asymmetric aldol reaction. They all include at least one metal centre acting as a Lewis acid, surrounded by a chiral environment. The first example, reported by Noyori *et al.* disclosed a new protocol using a simple diol-modified calcium catalyst that gave chiral aldol products with reasonable enantiomeric excess (Scheme 13).[57] The reaction of acetophenone **45** and pivaldehyde **46** was promoted by a catalyst system composed of $Ca[N\{Si(CH_3)_3\}_2]_2THF_2$ **47**, (*S*,*S*)-hydrobenzoin **48**, and KSCN **49**, in a ratio (1:3:1). After 20 hours in a solvent mixture of propionitrile:THF (4:1) at -20 °C, (*R*)-3-hydroxy-4,4-dimethyl-1-phenylpentan-1-one **50** was obtained in 74% yield with 89% ee.

Scheme 13. Asymmetric aldol reaction of acetophenone and pivaldehyde.



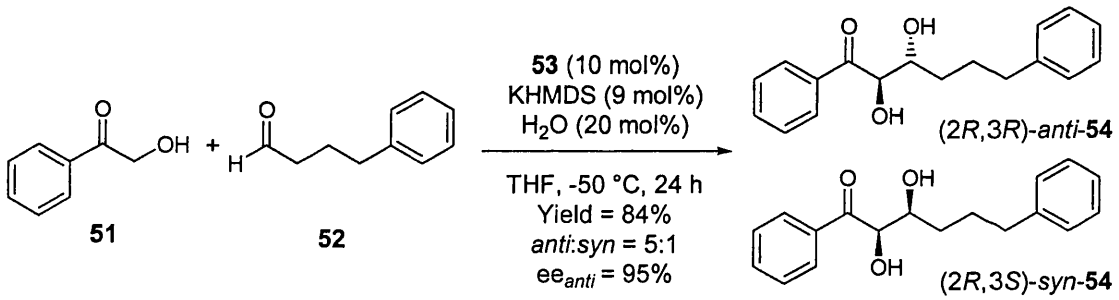
The reaction of aldehydes possessing bulky substituents like a tertiary alkyl group gave aldol products in good yields with excellent ee's (87-91%). However, the excess of ketonic substrate, typically 10 equivalents, was crucial to obtain the aldol product in a reasonable chemical yield and with a satisfactory ee (a one to one ratio of ketone to aldehyde at -20 °C for 160 hours gave the aldol adduct in only 20% yield and 77% ee). The excess ketone could be recovered by distillation.

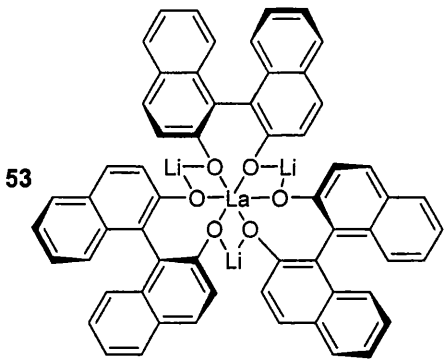
I 5B Shibasaki's LLB catalyst

Another effective catalyst for the direct asymmetric aldol reaction was reported by the group of Shibasaki.[58,59] In analogy to the class II aldolases, this heteropolymetallic catalyst, $LaLi_3$tris((*S*)-binaphthoxide) **53** and KOH ((*S*)-LLB)(KOH), had a cooperative mode of action. Shibasaki *et al.* used it in the synthesis of *anti*-α,β-dihydroxy ketones in an enantioselective manner (Scheme 14).[60,61] Potassium hydroxide was formed *in situ* by reaction of KHMDS and H_2O and was axially coordinated to the La cation. The envisaged catalytic cycle proposed was that a Brønsted base functionality in the catalyst ((*S*)-LLB)(KOH) deprotonated an α-proton

of the 2-hydroxyacetophenone **51** to generate a metal enolate, while at the same time, Lewis acid functionality activated the 4-phenylbutanal **52**. The latter then reacted with the metal enolate in a chelation controlled asymmetric environment to afford a *β*-keto metal alkoxide. Proton exchange between the metal alkoxide moiety and an aromatic hydroxy proton or an *α*-proton of a ketone could then lead to the generation of optically active aldol adducts (2*R*,3*S*)-*syn*-and (2*R*,3*R*)-*anti*-**54** and regeneration of the catalyst. The products were obtained in 84% yield after 24 hours at -50 °C in THF. The diastereomeric ratio was 5 to 1 in favour of the *anti*-diol. The enantiomeric excess of (2*R*,3*R*)-*anti*-**54** was 95%.

Scheme 14. Shibasaki's direct catalytic asymmetric aldol reaction.



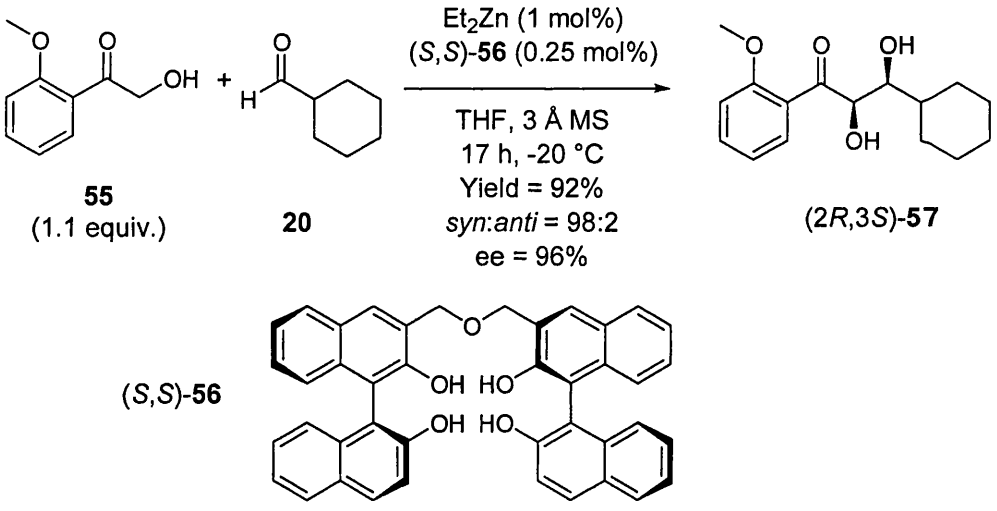


Several other reactions using this methodology were synthetically useful and were recently applied to the synthesis of Fostriecin, a potent and promising anticancer agent.[62]

I 5C Shibasaki's Et_2Zn / linked BINOL complex

Whilst the previous catalyst ((*S*)-LLB)(KOH) gave *anti*-diols selectively, Shibasaki *et al.* also provided a catalyst that furnished *syn*-diols.[60,63] In their first report, they used a 2 to 1 ratio of diethyl zinc (Et_2Zn) to chiral linked BINOL (*S*,*S*)-**56**. However, they obtained poor diastereoselectivity, despite the high yields and ee. Nevertheless, whilst clarifying the active catalytic species, thanks to their mechanistic studies, they discovered that a 4 to 1 ratio of Et_2Zn to (*S*,*S*)-**56** was an even more powerful catalyst (Scheme 15). Indeed, the addition of 2-hydroxy-2'-methoxyacetophenone **55** (1.1 equiv.) to one equivalent of cyclohexylcarboxaldehyde **20** was promoted by only 1 mol% of Et_2Zn and (*S*,*S*)-linked-BINOL **56** (0.25 mol%). After 17 hours at -20 °C, in the presence of 3 Å molecular sieves in THF, the (2*R*,3*S*)-*syn*-diol **57** was obtained in a 92% yield, and 96% ee. They were even able to decrease the catalyst loading to 0.4 mol% of Et_2Zn and 0.1 mol% of **56** without significant changes in the yield and ee.

Scheme 15. Shibasaki's asymmetric Zn catalysis.

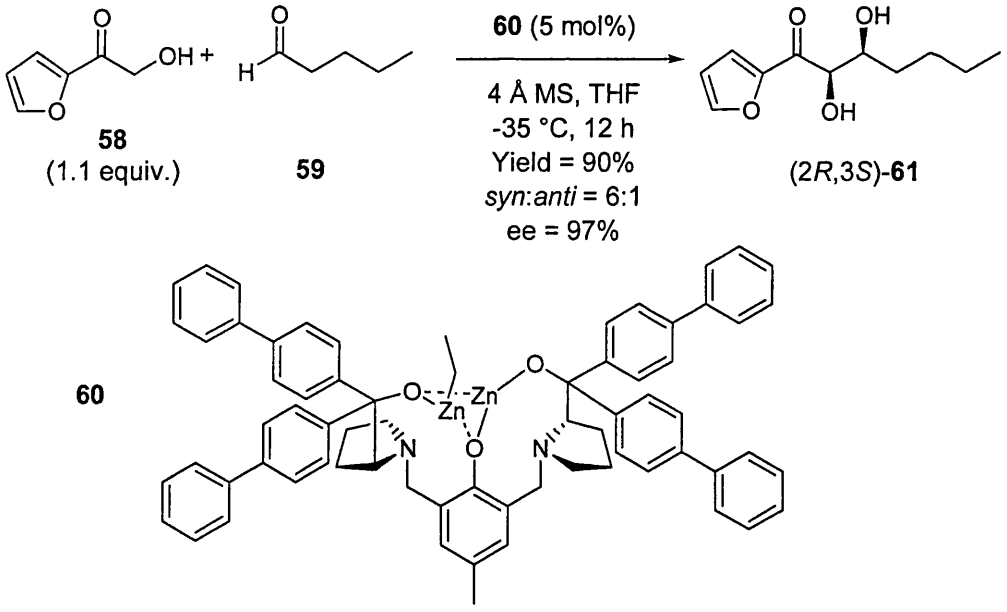


Following these results, they tried to form chiral quaternary carbon stereocentres but they had to increase the ketone loading to get reasonable yields (72-97% for linear aldehydes). The enantiomeric excesses were good to excellent (up to 97%) but eventually, the diastereomeric excesses were lower and the reaction did not proceed using α-substituted aldehydes like cyclohexylcarboxaldehyde **20**.

I 5D Trost's bimetallic Zn catalysts

In addition to Shibasaki's zinc catalyst, Trost *et al.* developed a binuclear catalyst **60** for *syn*-selective aldol reaction (Scheme 16).[64,65,66] The role of the two proximal zinc centres was to provide a first zinc to form the requisite enolate and a second one to function as a Lewis acid and coordinate to the aldehyde. These two zinc species were maintained together thanks to a semi-crown designed ligand that provided good chiral recognition.

Scheme 16. Trost's synthesis of the *syn*-diol intermediate of boronolide.



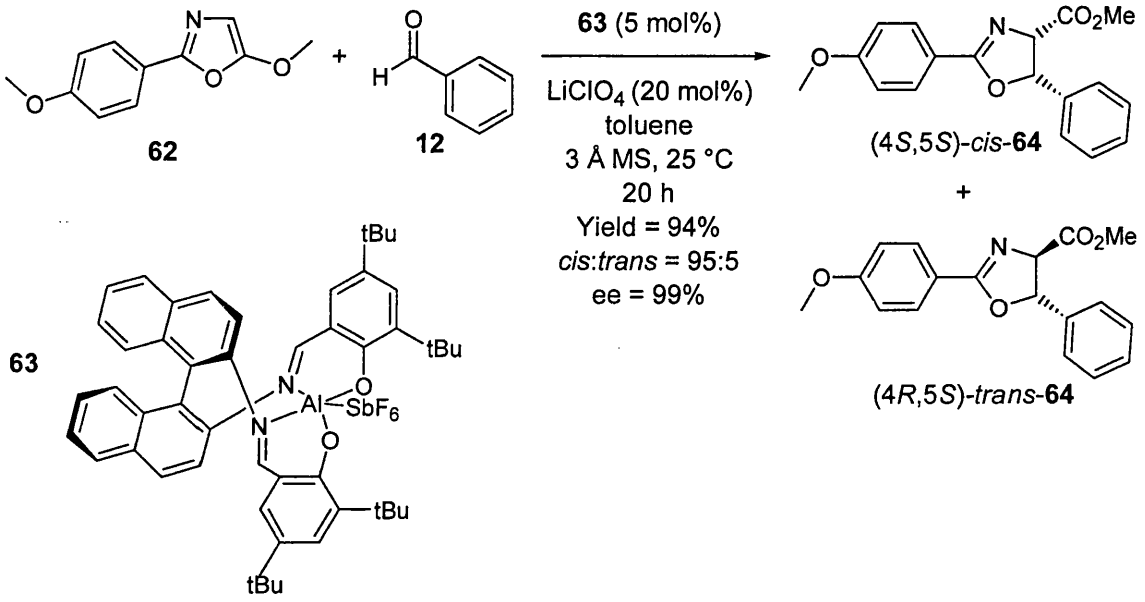
Initially, they used a high loading of one of the substrates and had to resort to additives like triphenylphosphine sulphide to improve the turnover and ee. Nevertheless, lowering the substrate loading ratio of ketone to aldehyde to (1.1:1.0) rendered the use of additives obsolete and improved both the diastereoselectivity and enantioselectivity. So did lowering the temperature of the reaction, albeit at the expense of conversion. Recently, they applied this novel di-zinc catalyst to the stereoselective synthesis of boronolide, a substance that could be effective against malaria.[67] The reaction required only 1.1 equiv. of ketone nucleophile **58** to add to valeraldehyde **59** (1 equiv.) and was completed within 12 hours at -35 °C in THF. The catalyst **60** (5 mol%) gave the best performance in terms of yield and selectivity in comparison with different aryl-substituted ligands. The aldol products were obtained in 90% yield, with a diastereoselectivity of 6 to 1 in favour of the *syn*-diol (2*R*,3*S*)-**61**, and 97% ee. Trost *et al.* proposed a catalytic mechanism for this reaction where the enolisation of the ketone nucleophile was largely *Z* and formed a bidentate ligand bridging the two zinc species. The bulk of the ligand exerted a great facial selectivity in the binding of the aldehyde furnishing the *syn*-diol. This catalyst has also been used with different substrates and gave excellent results in term of yield and selectivity.

I 5E Evans's new Al-catalysed asymmetric aldol reaction

The last recent report of an efficient direct asymmetric catalysis came from the group of Evans.[68] They discovered and characterised an aluminium complex **63** used to promote the catalytic synthesis of *cis*-cyclic diastereomers (4*S*,5*S*)-**64**, synthetic equivalents of α-amino-β-hydroxy acids (Scheme 17). Their best results were obtained by reacting the 5-methoxyoxazole **62** (1 equiv.) with benzaldehyde **12** (1.2 equiv.) and 5

mol% of the catalyst **63** in toluene, at 25°C, in presence of 3 Å MS, and 20 mol% of $LiClO_4$. This last additive was supposed to promote the breakdown of the aluminium alkoxide aldolate intermediate. The *cis*-cyclic product **64** was formed in a 94% yield, with a diastereomeric ratio of (95:5) and with an ee of 99%.

Scheme 17. Aluminium catalyst for the enantioselective aldol reaction.



The scope of aldehyde substrates was studied and extended to a wide range of aromatic compounds. The yields were all higher than 93%, the diastereomeric ratios were around 90:10 in favour of the *cis*-cyclised product. The ee's were all higher than 91% and mostly higher than 98%. Surprisingly, aliphatic aldehydes were found to be unreactive under the standard reaction conditions. An interesting advantage of this *cis*-cyclic product is that it could be epimerised to (4*R*,5*S*)-*trans*-**64** by treatment with a catalytic amount of DBU (*cis*:*trans* = 5:95, ee > 99%). This method has recently been successfully applied to the enantioselective total synthesis of the potent antimitotic agent ustiloxin D.[69] This aluminium catalyst, in addition to Trost's and Shibasaki's bimetallic catalysts and Noyori's calcium catalyst, are a few examples of catalysts for

the direct aldol reaction. In addition, soft enolisation, a mild method of enolisation, has also furnished access to aldols and is discussed in the next section.

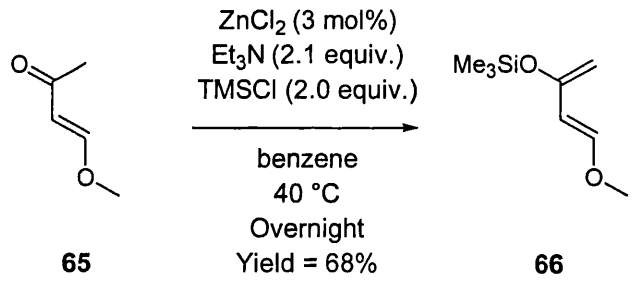
I 6 Soft enolisation

As detailed above, the need for a predictable aldol reaction led to the control of the geometry of the enolate nucleophile and the transition state. The Mukaiyama aldol reactions provide a powerful tool using preformed silyl enol ether of fixed geometry. However, this methodology lengthens the overall reaction sequence. In contrast, biological and related catalytic systems are good catalysts for the direct aldol reaction but tend to be substrate-specific and also generally require an excess of starting material to bias the equilibrium and to influence the product formation. Just a few catalysts have been recently developed for the direct asymmetric catalysis of the aldol reaction. A different strategy from those previously reviewed uses the concept of soft enolisation to generate *in situ* the nucleophile that can further react with an electrophile. The formation of the enolate is effected under mild conditions by the combination of a Lewis acid and a mild tertiary amine base. In this process, the Lewis acid first coordinates to the carbonyl oxygen and in doing so activates the α-hydrogen atoms to deprotonation. Crucially by using this protocol, a much weaker base than usual can be used. In the following sections, a few examples of soft enolisation developed in the past will be discussed. This will lead us to the proposal of a new methodology for the asymmetric catalytic aldol reaction.

I 6A Danishefsky's diene

An impressive example of the use of soft enolisation conditions was reported by Danishefsky and co-workers.[70] In their quest for different functionalities and oxidation levels of dienes for the Diels-Alder reactions, they wanted to obtain 1,3-dialkoxybutadienes. Pyrolysis of 1,1,3,3-tetramethoxybutane gave unsatisfactory results. However, reaction of **65** with TMSCl in the presence of triethylamine and zinc chloride overnight at 40 °C gave a 68% yield of *trans*-1-methoxy-3-trimethylsilyloxybuta-1,3-diene **66** (Scheme 18). Importantly, in the absence of the zinc chloride Lewis acid, no enolisation of **65** occurred.

Scheme 18. Danishefsky's diene formation.

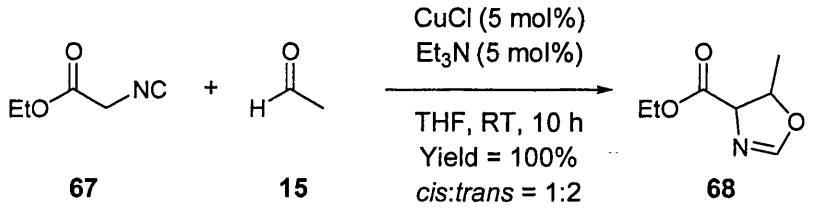


I 6B Ito's CuCl/Et_3N and Au(I)/R_3N catalysts

Following Danishefsky's use of soft enolisation, the group of Ito reported two aldol reactions using a similar process. While studying an aldol reaction promoted by a stoichiometric amount of zinc chloride, they found out that a catalytic amount of copper(I) chloride was enough to induce the reaction of isocyanoacetate with α,β-unsaturated aldehydes.[71] In the case of *trans*-cinnamaldehyde, the reaction was taking up to two days. However, it was noted that the addition of one equivalent of an amine to

the catalyst caused remarkable acceleration of the reaction rate. Indeed, the reaction of ethyl isocyanoacetate **67** with acetaldehyde **15** in the presence of 5 mol% of CuCl and 5 mol% of TEA in THF was completed in 10 hours at RT (Scheme 19). The 4-ethyloxycarbonyl-5-methyl-2-oxazoline **68** was obtained as a (1:2) mixture of the *cis*- and *trans*-diastereomers.

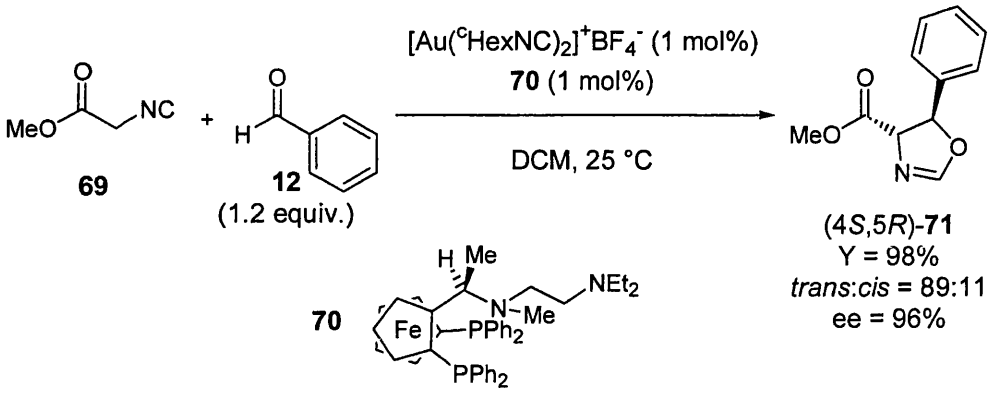
Scheme 19. Ito's catalytic formation of oxazoline.



They also noted that changing TEA for the chiral amine (1*R*,2*S*)-(-)-ephedrine developed some asymmetric induction, but did not report any ee value.

Afterwards, Ito, Hayashi *et al.* disclosed a chiral ferrocenylphosphine-gold(I) complex for the catalysis of asymmetric aldol reaction.[72] This complex was generated by mixing bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate (1 mol%) acting as a Lewis acid and a chiral phosphine ligand, (*R*)-*N*-methyl-*N*-[2-(diethylamino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]-ethylamine **70** (1 mol%). The ligand was also playing the role of the weak base due to the tertiary amine substituent (Scheme 20). This catalyst was applied to the soft enolisation of methyl isocyanoacetate **69** (1 equiv.). The gold enolate was then trapped by benzaldehyde **12** (1.2 equiv.) to afford the (4*S*,5*R*)-4-(methyoxycarbonyl)-5-phenyl-2-oxazoline **71** in 98% yield, with a good diastereoselectivity (*cis*:*trans* = 11:89) and an excellent ee for (4*S*,5*R*)-*trans*-**71** (96%). This gold catalyst was also effective for the reaction with various aliphatic aldehydes.

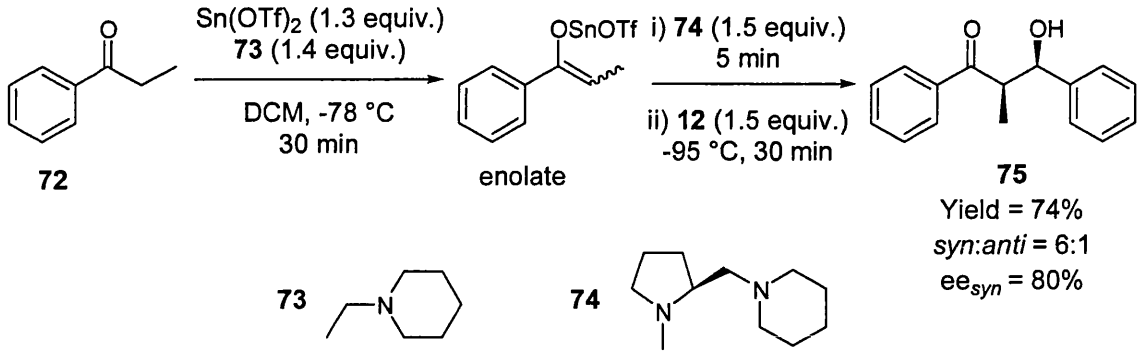
Scheme 20. Ito's Au(I)/R_3N soft enolisation system.



I 6C Mukaiyama $Sn(OTf)_2$/*N*-ethylpiperidine system

Aside to the Mukaiyama aldol reaction using preformed silyl enol ethers, Mukaiyama *et al.* reported an aldol reaction that proceeds through a transient enolate formed by soft enolisation.[73] They found that a stoichiometric amount of $Sn(OTf)_2$ in combination with *N*-ethylpiperidine **73** in DCM at -78 °C was promoting the enolisation of propiophenone **72**. Subsequently they trapped this tin enolate with different aldehydes and obtained aldol adducts in good yields and *syn*-diastereoselectivity. Moreover, they discovered that the addition of a chiral chelating diamine prior to the addition of the trapping agent was generating a chiral enolate (Scheme 21).[74] Propiophenone **72** was enolised under mild kinetic conditions by $Sn(OTf)_2$ (**1**.3 equiv.) and *N*-ethylpiperidine **73** (1.4 equiv.) in DCM at -78 °C for 30 minutes to give the tin enolate. The metal centre was then rapidly (5 minutes) coordinated by the chiral diamine (*S*)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine **74** (1.5 equiv.) and reacted at -95 °C with benzaldehyde **12** (1.5 equiv.). After 30 minutes, the 3-hydroxy-2-methyl-1,3-diphenyl-1-propanone **75** was obtained in 74% yield, in a 6:1 *syn*:*anti* mixture with 80% ee for the *syn*-adduct.

Scheme 21. Sn(II)/*N*-ethylpiperidine soft enolisation.

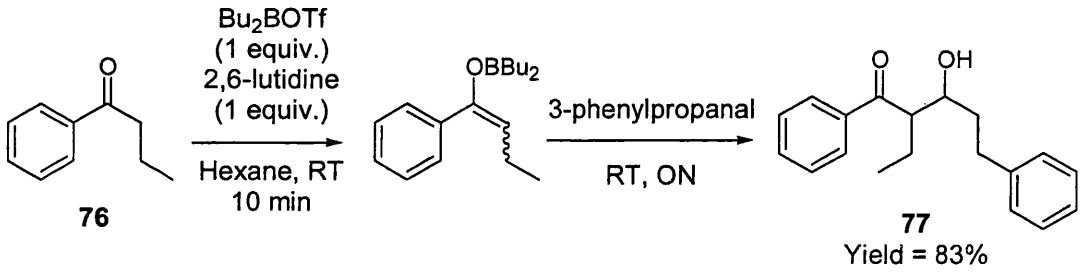


This was the first reported example of highly enantioselective cross aldol reaction of metal enolate generated *in situ* from ketone. The enantioselectivity was lower than for the direct aldol reactions of the previous section (I 5). Later, Evans *et al.* successfully applied this technique to the soft enolisation of chiral imides and *β*-keto imides forming aldol adducts with diastereoselectivity greater than 99%.[10]

I 6D Boron enolate formation by soft enolisation techniques

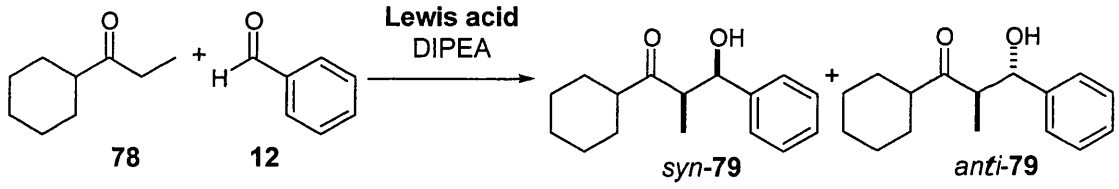
In addition to the soft enolisation mediated by $Sn(OTf)_2$ and a tertiary amine base, Mukaiyama also reported the soft enolisation of ketones and *in situ* formation of vinyloxyboranes.[75,76,77] Under mild conditions (2,6-lutidine), the ketone **76** reacted with the dibutylboron triflate to form a vinyloxyborane (Scheme 22). The formed enolate then reacted with 3-phenylpropanal to yield the aldol product **77** in 83% yield. They also noticed that lowering the temperature to -78 °C favoured the cross aldol reaction and reduced the isomerisation of the enolate. However, they did not report any diastereoselectivity or geometry of the formed enolate, which prompted Masamune and Evans into developing this process.

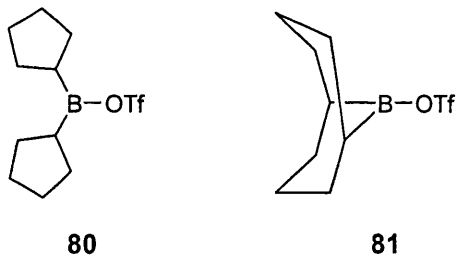
Scheme 22. Soft enolisation of ketone **76** into vinyloxyborane.



Masamune *et al.* first studied the formation of the enolate with various substituents on the boron triflate and used them for the aldol reaction.[78] They reported sterical interactions influencing the geometry of the enolate. Depending on the boron triflate used, dicyclopentyl boron triflate **80** or 9-borabicyclo[3.3.1]non-9-yl (9-BBN) **81**, they obtained complementary results (Table 4). Treatment of cyclohexyl ethyl ketone **78** with **80** and diisopropylethylamine gave preferentially the (*E*)-enolate and after trapping by benzaldehyde **12** yielded the *anti*-isomer **79** with a *syn*:*anti* ratio of (15:85). However, changing the boron triflate for **81**, resulted in the opposite diastereoselectivity (*syn*:*anti* = 97:3).

Table 4. Masamune *syn*- or *anti*-selective aldol reaction.



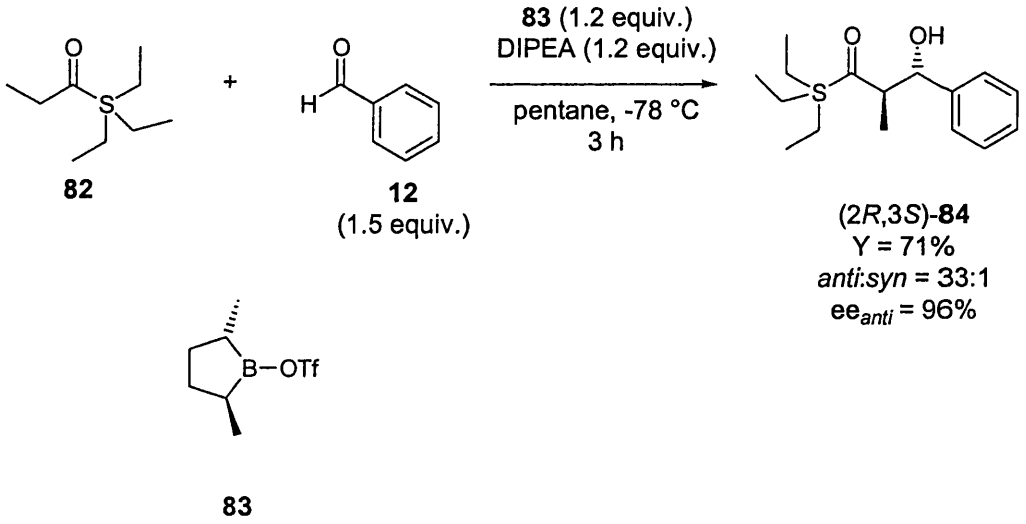


80 81

Entry	Lewis acid	*syn-anti*	Yield (%)
1	**80**	14/86	88
2	**81**	97/3	79

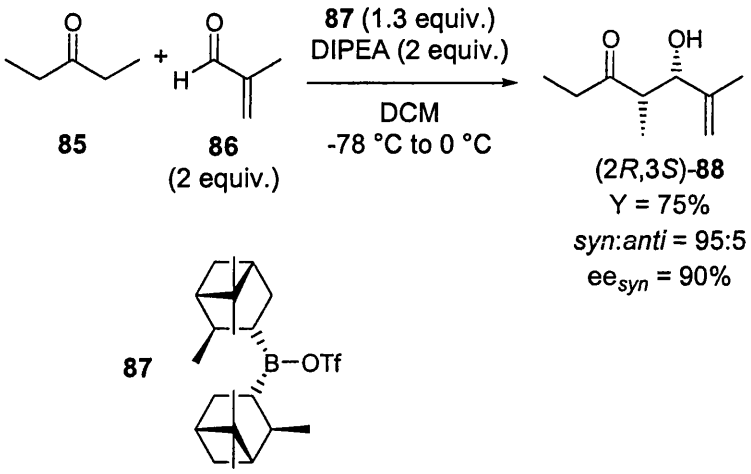
Later, Masamune and co-workers used the chiral boron triflate **83** in an enantioselective *anti*-selective aldol reaction (Scheme 23).[79] Stoichiometric soft enolisation of a *S*-3-(3-ethyl)pentyl propanethioate **82** by the boron triflate **83** and Hünig's base afforded, after treatment with benzaldehyde **12** (1.5 equiv.), the aldol adduct in good yield (71%), in favour of the *anti*-diastereomer (2*R*,3*S*)-**84** (*syn*:*anti* = 1:33) and excellent ee (96%). This reaction is proposed to proceed through the formation of an (*E*)-boron enolate which then coordinates to an aldehyde and reacts in a chair-like transition state.

Scheme 23. Masamune's enantioselective and *anti*-selective aldol reaction.



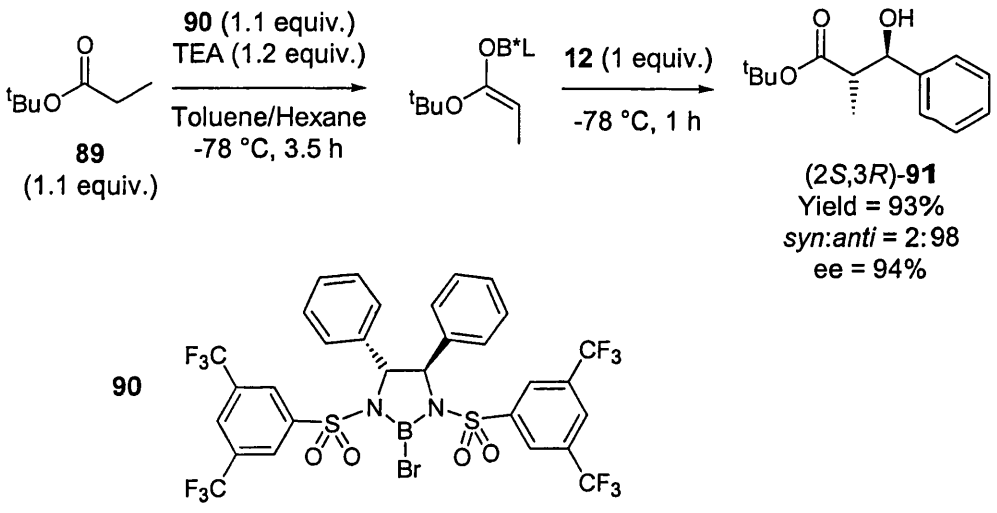
Paterson *et al.* developed a similar system using the chiral boron triflate **87** in combination with DIPEA for the *syn*-selective aldol reaction of diethylketone (Scheme 24).[80,81] They used different chiral alkyl substituents and (-)-isopinocampheyl gave the best diastereo- and enantioselectivity. The chiral (*Z*)-boron enolate was preferentially formed (> 10:1) and one of its faces was discriminated due to the presence of the chiral ligands. The aldol adduct **88** was then obtained, after addition of the aldehyde **86** (2 equiv.) and oxidative work-up, in good yield (75%) and good ee (90%).

Scheme 24. Paterson's chiral boron agents.



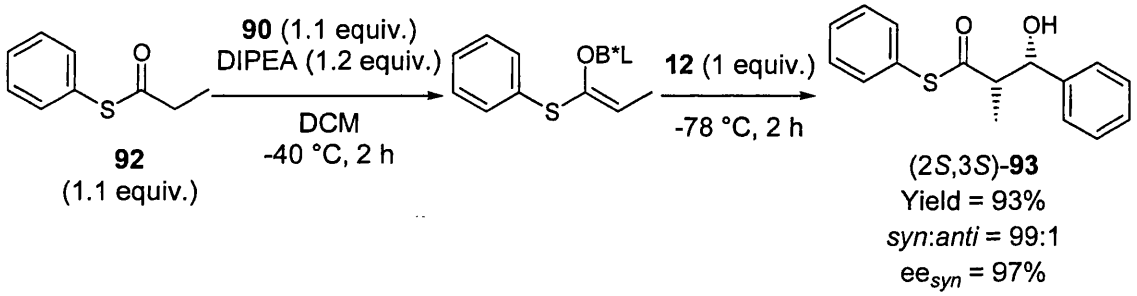
Corey *et al.* developed a system based on the chiral boron bromide **82** (Scheme 25).[82] Depending on the substrate used and the base promoting the enolisation, they obtained the opposite diastereoselectivity. For example, the soft enolisation of *tert*-butyl ester **89** by the boron bromide **90** and TEA in a 1 to 2 mixture of toluene hexane at -78 °C for 3.5 hours afforded the (*E*)-enolate and subsequent reaction with benzaldehyde **12**, still at -78 °C, for 1 h, furnished the aldol adduct (2*S*,3*R*)-**91** in 93% yield, in excellent diastereoselectivity (*syn*:*anti* = 2:98) and excellent ee (94%).

Scheme 25. Use of Corey's versatile *anti*-selective reagent.



Nevertheless, the soft enolisation of *S*-phenyl thiopropionate **92** by the same boron bromide **90** but using DIPEA in DCM, at -40 °C for 2 h, gave preferentially the (*Z*)-enolate and then the *syn*-aldol adduct (2*S*,3*S*)-**93** by reaction with benzaldehyde **12** (93% yield, *syn*:*anti* = 99:1, 97% ee) (Scheme 26).

Scheme 26. Corey's *syn*-selective aldol reaction.

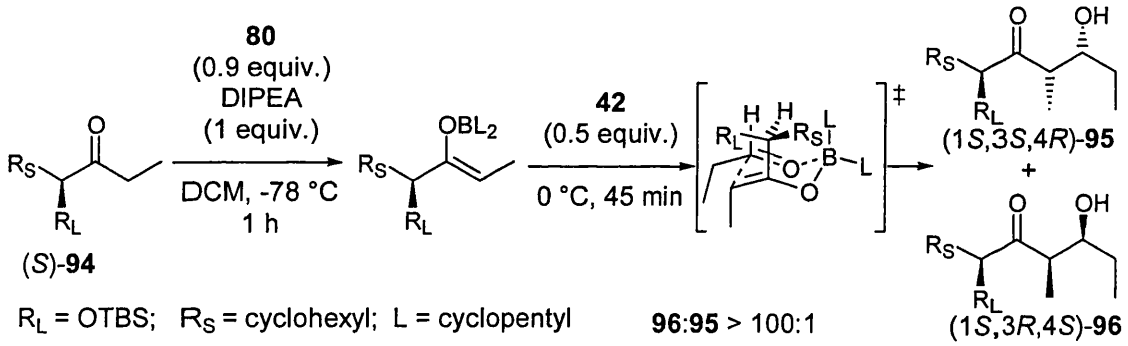


The counter ions of the Lewis acid used for the previous soft enolisations generating boron enolates were either triflates or bromides. Regardless of the nature of the anion, the selective formation of (*Z*)- or (*E*)-enolates was reported. However, Brown *et al.* noticed an effect of the leaving group over the geometry of the enolate.[83,84] They observed that the formation of (*Z*)-enol borinates was favoured by boron Lewis acid with good leaving groups, such as triflate, mesylate and iodide. On the contrary, Lewis acids with poorer leaving groups, such as bromide and chloride favoured the formation of (*E*)-enol borinates.

One last interesting aspect of the boron mediated soft enolisation was the formation of chiral enolates from chiral substrates and their use in the asymmetric aldol reaction. Both Masamune and Evans reported different interesting substrates. An important change reported by Evans *et al.* was the fact that in boron enolates the metal-oxygen bond is shorter (*ca.* 1.4 Å) than in any other commonly used metal enolates (1.9-2.2 Å). The same bond length reduction was observed between the boron and the

carbon atoms. As emphasised by Evans and co-workers in a comparison of the diastereoselectivity of various aldol products obtained from lithium, aluminium and boron enolates, the latter gave smaller and tighter transition state and therefore a better stereoselectivity.[85] Evans *et al.* subsequently reported the first enantioselective aldol condensation *via* boron enolates of (*Z*)-geometry.[86] The chiral ketone was formed from (*S*)-proline and gave after removal of the chiral auxiliary *syn*-aldol adducts with ee's up to 94%. Based on the same considerations and transition states, Masamune *et al.* reported a more stereoselective aldol reaction using chiral boron enolates (Scheme 27).[87] Firstly, the ketone **94** was enolised under mild conditions by dicyclopentylboron triflate **80** and DIPEA in DCM under kinetic conditions to generate the (*Z*)-enolate.

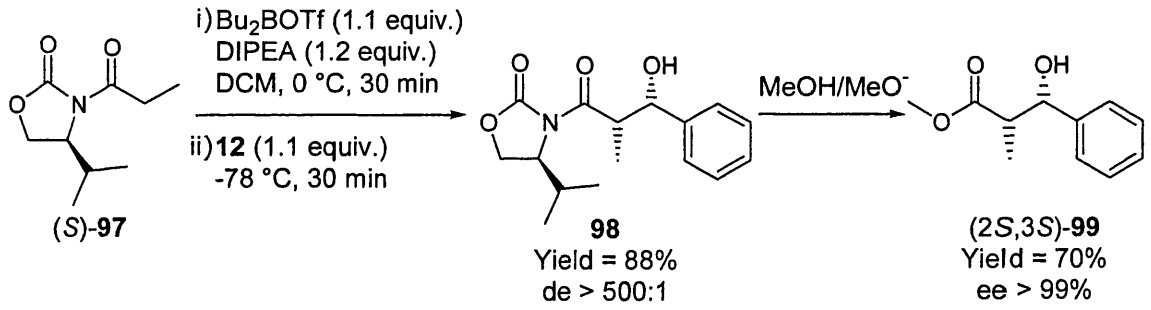
Scheme 27. Chiral induction from a chiral silyloxyketone.



Trapping by propanal **42**, gave rise to the *anti,syn*-diastereomer (1*S*,3*S*,4*R*)-**95** and *syn,syn*-diastereomer (1*S*,3*R*,4*S*)-**96** in *ca.* 80% yield (**96**:**95** > 100:1). No trace of the *anti,anti*- or *syn,anti*-adducts could be detected. The auxiliary was removed by treatment with HF in acetonitrile followed by oxidation to give the *β*-hydroxy acid without epimerisation. The formation of the all *syn*-diastereomer (1*S*,3*R*,4*S*)-**96** was rationalised by a pericyclic transition state where the non-bonded interactions between the ligands and the chiral auxiliary on the ketone were minimised (Scheme 27).

Finally, the soft enolisation of imides reported by the Evans group was a seminal work on chiral auxiliaries.[88] The enolisation of the *N*-propionylimide (*S*)-**97** was mediated by a stoichiometric amount of dibutylboron triflate and the weak base DIPEA (Scheme 28). Under kinetic conditions, the (*Z*)-enolate was obtained selectively (*Z*:*E* > 100:1). The boron enolate was then reacted with various aldehydes, which gave good results for both aromatic and aliphatic aldehydes. On reaction with benzaldehyde **12**, at -78 °C after 30 minutes, the *β*-hydroxyimide adduct **98** was obtained in 88% yield with a diastereoselectivity greater than 500:1. The adduct could be directly transformed into the corresponding methyl ester (2*S*,3*S*)-**99** by treatment with sodium methoxide in anhydrous methanol (Yield = 70% and ee > 99%).

Scheme 28. Asymmetric induction using chiral oxazolidones.

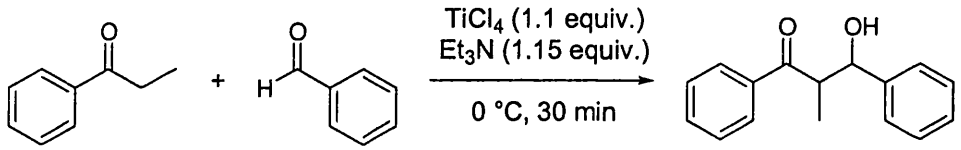


No racemisation of either stereogenic centre was observed. Importantly, the chiral auxiliary could be recycled after the reaction. The opposite configuration of this *syn*-aldol could be accessed by using an auxiliary of opposite configuration. These methods and more particularly Evans's and Paterson's are constantly used for the synthesis of molecules that are of biological interest.[89,90] In addition to these powerful soft enolisations mediated by boron salts and tertiary amines, the enolisations promoted by titanium(IV) Lewis acids in conjunction with tertiary amines have given excellent results and are presented in the next section.

I 6E Soft enolisation promoted by Ti (IV)/weak amine base

In 1970, Lehnert reported the first soft enolisation using Ti(IV) (2 equiv.) and pyridine (4 equiv.) for a variant of the Knoevenagel condensation.[91] Then Harrison developed a stoichiometric soft enolisation technique.[92] He reported the *in situ* generation of titanium enolates of acetophenone, propiophenone and isobutyrophenone and their trapping with aromatic aldehydes. The deprotonation of propiophenone **72** (1 equiv.) was effectuated by 1.1 equivalents of titanium tetrachloride and 1.15 equivalents of triethylamine at 0 °C in DCM (Scheme 29).

Scheme 29. Transient titanium enolate aldol condensation.



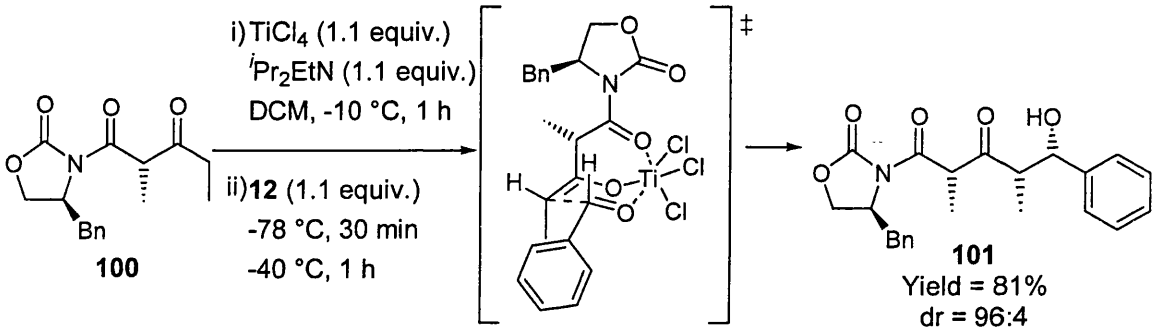
72 **12** **75**
Yield = 91%
syn:*anti* = 95:5

These conditions were supposed to provide a preponderance of the (*Z*)-enolate and gave as rationalised by a Zimmerman-Traxler chair-like transition state, by reaction on benzaldehyde **12**, the racemic *syn*-aldol adduct **75** in 91% yield and 95:5 *syn*:*anti* diastereoselectivity. What is noteworthy is the exclusion of either $TiCl_4$ or TEA resulted in no product formation.

As mentioned earlier, Evans *et al.* reported soft enolisation of *β*-keto imides with $Sn(OTf)_2$ and TEA.[10] At the same time, they disclosed soft enolisation conditions and reaction with various aldehydes giving the all *syn* complementary diastereomer (Scheme 30). The reaction of the *β*-keto imide **100** with a stoichiometric amount of

$TiCl_4$ and TEA in DCM for 1 hour at -10 °C afforded the (*Z*)-trichlorotitanium enolate, which provided exceptional levels of asymmetric induction in the aldol addition to benzaldehyde **12** to give the all-*syn* adduct **101** in 81% yield and 96:4 diastereomeric ratio. The chelated transition state in scheme 30 is consistent with the observed stereochemical outcome of the reaction.

Scheme 30. All *syn*-diastereoselective aldol reaction using *β*-keto imide.

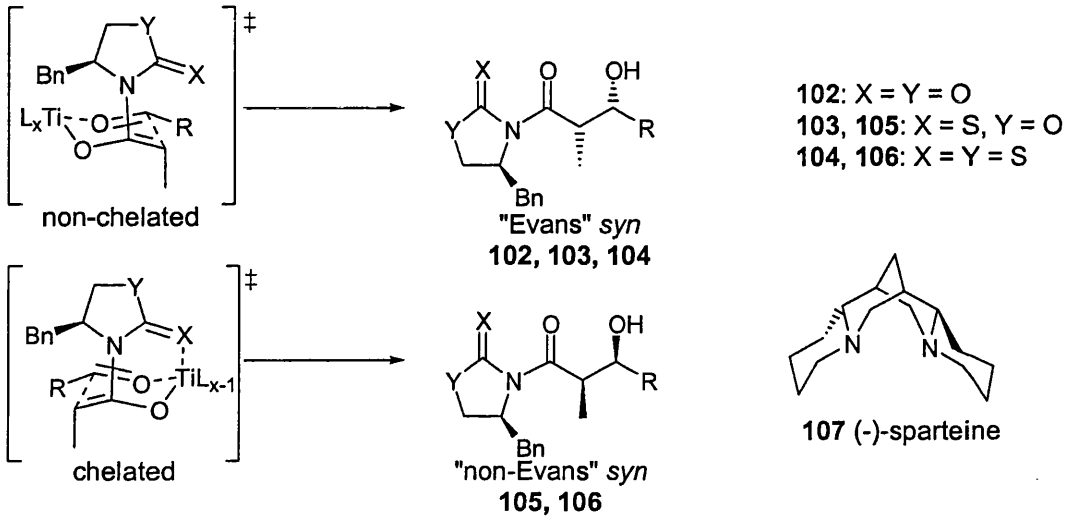


Later, Evans *et al.* extended this methodology to other enolate precursors that were reacted with various electrophiles (acetals, alkylating agents and Michael acceptors).[93,94] Cinquini, Cozzi and co-workers adapted this technique to the soft enolisation of thioesters and *α*-substituted esters.[95]

Recently, Crimmins's group has extended the Evans's titanium methodology and studied the influence of the Lewis acid stoichiometry as well as the addition of a chelating ligand or the use of different chiral auxiliaries, on the formation of both the *syn*-aldols.[96] They first noticed that changing the base, DIPEA for (-)-sparteine **107** drastically improved the soft enolisation of *N*-acyl oxazolidinone, oxazolidinethione and thiazolidinethione by $TiCl_4$. The chiral enolates were generated and reacted with an aldehyde (1.1 equiv.) within a few minutes through a cyclic transition state to afford both the "Evans" *syn*-**102**, **103** and **104** and the "non-Evans" *syn*-**105** and **106** adducts.

The major difference was the possibility for the auxiliary to chelate the Lewis acid (scheme 31).

Scheme 31. Crimmins's asymmetric aldol additions.



Regarding the *N*-acyloxazolidinone, the "Evans" *syn*-adduct **102** was obtained in good yield and selectivity, due to a non-chelated cyclic transition state. The soft enolisation was effectuated by a stoichiometric amount of $TiCl_4$ and 2.5 equiv. of the base **107**. *N*-acyloxazolidinethione and *N*-acylthiazolidinethione were thought to chelate the Lewis acid but in fact, under similar enolisation conditions, the "Evans" *syn*-adduct **103** and the "Evans" *syn*-adduct **104** were obtained in good yields and selectivities. The formation of "non-Evans" *syn*-adduct **105** from *N*-acyloxazolidinethione was only possible when using 1 equivalent of base **107** and 2 equivalents of $TiCl_4$. The product was formed in good yield and selectivity. They proposed that a bimetallic catalyst where one of the chlorine atoms is shared by one of the two titanium atoms was generated *in situ* from $TiCl_4$ and allowed the coordination of the oxazolidinethione auxiliary to the other titanium Lewis acid. For the *N*-acylthiazolidinethione, the formation of "non-Evans" *syn*-adduct **106** was possible when only one equivalent of

base was utilised. The coordination of the thiocarbonyl of the thiazolidinethione was this time allowed by the lack of a second equivalent of **107** usually acting as a ligand. The yields and stereoselectivities of this aldol reaction were good using a range of aliphatic and aromatic aldehydes.

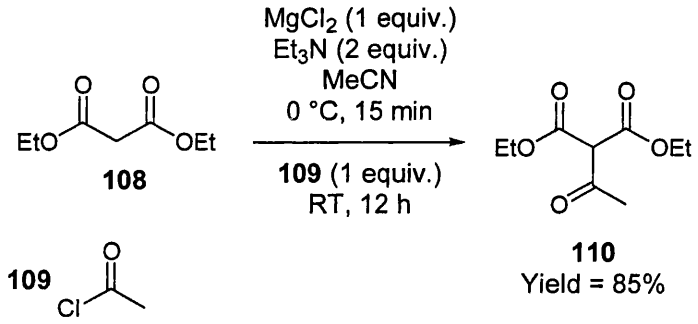
Recently, Crimmins *et al.* have also reported the diastereoselective formation of *anti*-glycolate aldol products mediated by the 4-benzyl-oxazolidine-2-thione auxiliary and two equivalents of $TiCl_4$ and (-)-sparteine **107**.[97] The addition of the enolate occurs *via* an open transition state with the glycolyl oxygen coordinated to the metal, activating the aldehyde. As exemplified, above, titanium based soft enolisation has been an effective technique and furnish selective *syn*- or *anti*-aldol products. Crimmins's technique was recently used for the synthesis of (*9S*)-dihydroerythronolide A **1** (Section I 1A, figure 1). All the soft enolisation methodology developed around Ti(IV) employed stoichiometric amounts, or greater, of Lewis acid and base. In the next section, a different Lewis acid, Mg(II) is used and only catalytic amounts are required in the last example.

I 6F Soft enolisation promoted by Mg(II) Lewis acids

The last soft enolisation techniques reviewed here used magnesium(II) as a Lewis acid. The aim of these reactions this time was not the aldol reaction but an acylation reaction, a carboxylation and a conjugate addition to nitroalkenes. Rathke and co-worker first reported a mild procedure for the acylation of diethyl malonate **108** with acid chlorides using tertiary amine bases and magnesium chloride.[98] The best conditions for the soft enolisation of **108** were deprotonation by TEA (2 equiv.) in conjunction with $MgCl_2$ (1 equiv.), in acetonitrile at 0 °C for 15 minutes (Scheme 32). Then the

acetyl chloride **109** was allowed to react for 12 h at RT. The product **110** was obtained in 85% yield.

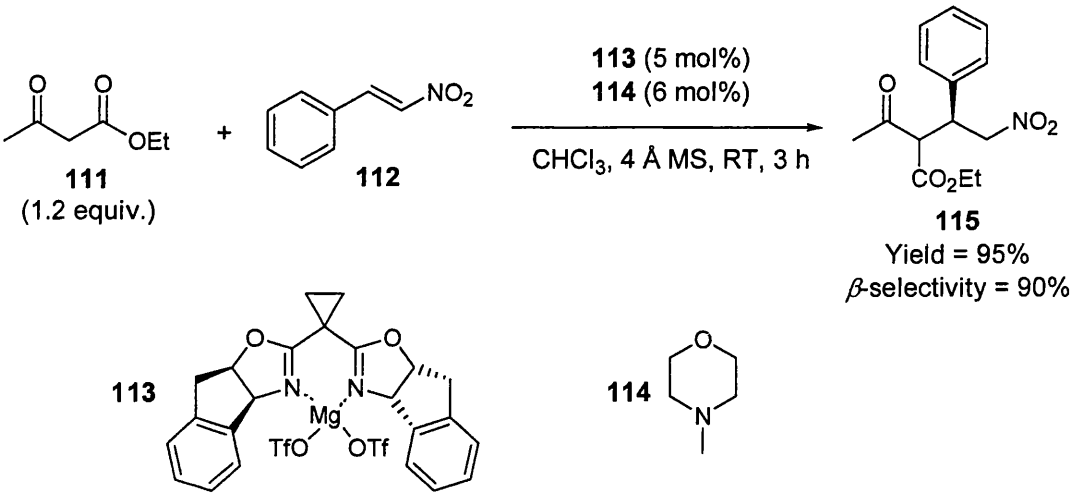
Scheme 32. Acylation of diethyl malonate.



Importantly, without either $MgCl_2$ or TEA no acylation was observed. This reaction was then extended to few other acyl chlorides and to ethyl acetoacetate. Rathke reported the carboxylation of ketones using TEA and magnesium halides.[99] He reported the preparation of β-keto acids from ketones with yields as high as 90%. The best result was obtained using 4 equivalents of TEA and 2 equivalents of Lewis acid ($MgCl_2$ + 2 NaI).

In a study on the epimerisation of chlorophyll derivatives, Watanabe *et al.* reported a synergistic action of TEA and $MgCl_2$ in the enolisation rate of pheophytin A and A'.[100] Under soft enolisation conditions, epimerisation rate constants were two orders of magnitude higher than when only $MgCl_2$ or TEA was present. However a real improvement in soft enolisation promoted by magnesium was reported by Ji, Barnes and co-workers.[101,102] They discovered that the complex **113** of magnesium triflate with the chiral bisoxazoline ligand and *N*-methylmorpholine **114** was an effective catalyst for the conjugated addition of ethyl acetoacetate **111** (1.2 equiv.) to nitrostyrene **112** (scheme 33).

Scheme 33. Catalytic soft enolisation promoted by Mg(II).



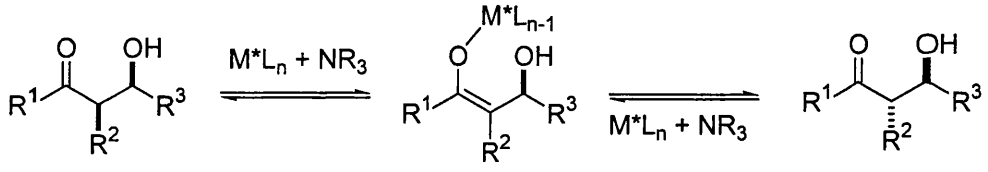
Only 5 mol% of this catalyst was sufficient to form the adduct **115** in 95% yield after 3 hours at RT in chloroform. In the absence of the base, NMM, the conversion was halved even after 15 hours. Notably, in the absence of the ligand, the reaction did not proceed and changing the Lewis acid gave lower yields or no reaction at all. The *β*-selectivity of this reaction was good. Nevertheless, under these reaction conditions, the ester bearing stereogenic centre was rapidly epimerised leading to a mixture of diastereomers. The good results obtained by soft enolisation techniques and the encouraging results reported by Ji and Barnes prompted us in the development of a method for the catalytic generation of chiral enolates and subsequent trapping using aldehydes.

I 7 Presentation of the project

Enolate-electrophile bond constructions are among the most efficient and general strategies for the stereoselective formation of carbon-carbon bonds in organic synthesis. The aldol addition reaction being the most utilised. As seen in section I 1, the numerous examples of the use of the aldol reaction in complex natural product

syntheses are testament to its general utility and practicability. Accordingly, there are many examples of diastereoselective aldol reactions that employ stoichiometric chiral controllers to ultimately deliver enantiomerically enriched adducts. Examples of catalytic enantioselective aldol reactions are scarcer, however several research groups have enjoyed considerable success in developing catalytic enantioselective variants of the Mukaiyama aldol reaction. In such reactions, which employ a latent enolate equivalent, the enantioselectivity originates from the use of a chiral Lewis acid catalyst. The catalyst functions *via* the formation of a transient chiral electrophile and mediates the bond-forming process. The formation of the enolate equivalent takes place in a separate operation. A more attractive strategy is to deliver the same bond construction by an aldol reaction incorporating enolate generation as an integral part of the catalytic cycle. This requires the catalyst to mediate both enolisation and subsequent bond formation. Such reactions proceed *via* the catalytic formation of a chiral nucleophile that could be obtained by soft enolisation conditions as discussed in section I 6. Unfortunately for Ji and Barnes, a one to one mixture of diastereomers was obtained (I 6E, scheme 33). This arose because the pK_a of the substrate and product were similar allowing enolisation of the product and epimerisation (Scheme 34).

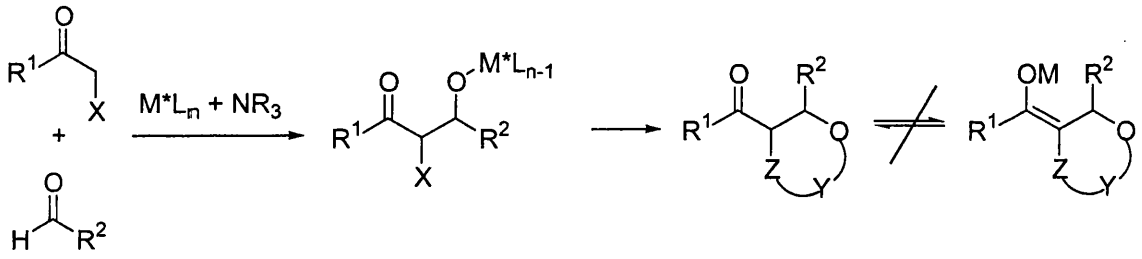
Scheme 34. Epimerisation of the α-carbon centre.



A solution to this problem would be to tune the selectivity of the base so that a small difference in acidity between the substrate and the product α-protons would be

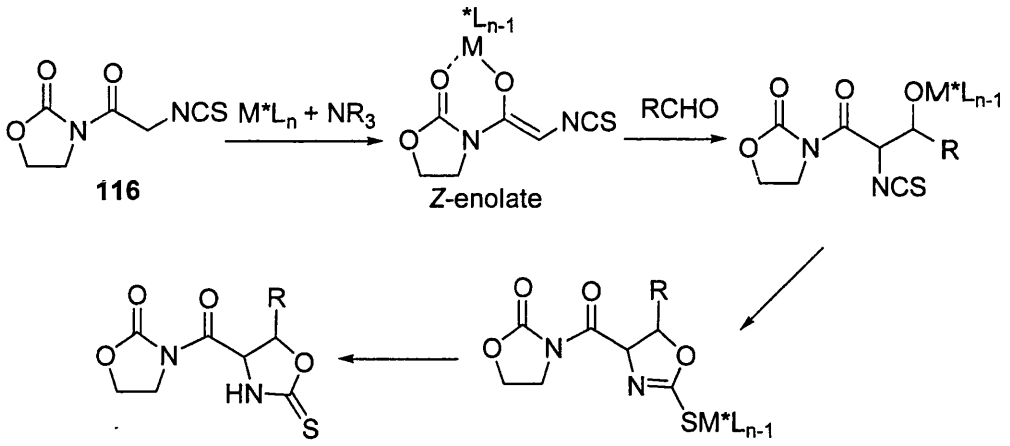
sufficient to limit product deprotonation. Usually the difference is too small and an alternative solution is to derivatise the product *in-situ* so that the pK_a of the proton α to the carbonyl group in the product is less acidic. This requires an α-substituent that can be modified post carbon-carbon bond formation, most likely by reaction with the alkoxide oxygen (Scheme 35).[72] Incorporating the newly formed hydroxyl group in a cyclic structure would also reduce the opportunity of product inhibition that could occur with a free β-hydroxy-carbonyl unit.

Scheme 35. Product derivatisation.



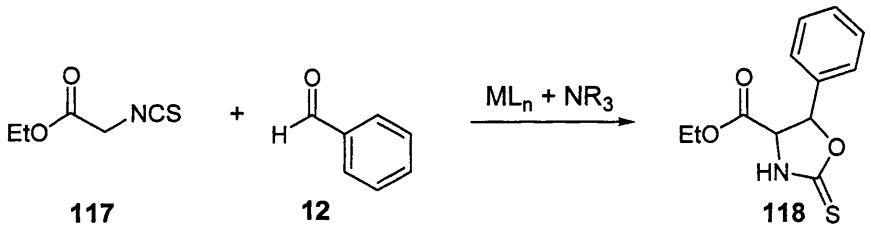
Isothiocyanate substituted *N*-acyl oxazolidinone **116** satisfies many of the required design criteria (Scheme 36). The isothiocyanate significantly attenuates the pK_a of the substrate, while following carbon-carbon bond formation, reaction with the newly generated alkoxide to form an oxazolidinethione is possible.[10,103,104,105] The α-proton present in the final product will have a higher pK_a than the starting substrate **116**. The basicity of the metalled thiooxazolidinone intermediate should be sufficient to regenerate the free base thus allowing the use of catalytic amounts of Lewis acid and base.

Scheme 36. Proposed isothiocyanatoacetate substituted imide enolisation and trapping.



One of the key objectives in establishing such a catalytic cycle is that the enolates produced are effective in transferring the chiral information from the catalyst to the incipient bond. *N*-acyloxazolidinones are known to selectively form (*Z*)-enolates, this, together with their bidentate nature results in rigid structurally well-defined enolates. Finally and of crucial importance is that the ultimate products of the catalytic cycle are synthetically useful stereo-defined protected β-hydroxy-α-amino acids. Early studies focussed on identifying suitable Lewis acid – base combinations that would effect deprotonation and allow completion of the catalytic cycle. In selecting these combinations, it was essential that the Lewis acid and the amine base did not form an irreversible adduct. Initial screenings were effectuated on a commercially available starting material ethyl isothiocyanatoacetate **117** in combination with the non-enolisable benzaldehyde **12** and formed the substituted oxazolidinethione **118** (Scheme 37).

Scheme 37. Initial screening for the soft enolisation.



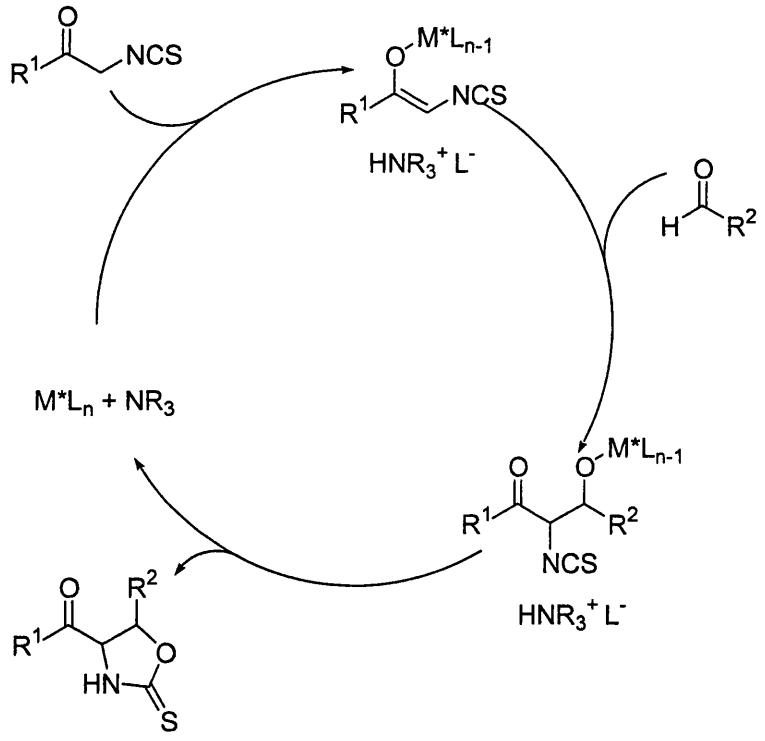
Once we set the catalytic conditions for the formation of the oxazolidinethione **118** and extended them to various aromatic aldehydes, we intended to study the transfer of stereochemical information from a chiral ligand to the product. We used both ester **117** and imide **116**, and obtained good yields with excellent stereoselectivities with benzaldehyde **12**. We also started to extend the project using different electrophiles such as aliphatic aldehydes, α,β-conjugated aldehydes and imines.

II Results and Discussion

II 1 Introduction

Many efficient asymmetric catalytic aldol reactions have been developed over the last 30 years. With the exception of the recently developed bimetallic catalysts, a preformed enolate is normally a prerequisite. Additionally, one of the substrates is generally added in large excess to drive the reaction to completion. Therefore, a new study on the asymmetric catalytic aldol reaction has been undertaken. To avoid the use of a preformed enolate the process of soft enolisation has been considered. The first stage was to identify the catalytic conditions for this aldol reaction (Scheme 38).

Scheme 38. Proposed asymmetric catalytic cycle for aldol reaction.



In order to differentiate the pK_a of the substrate and of the adduct, efforts focussed on a readily available starting material, ethyl isothiocyanatoacetate **117**, that undergoes cyclisation after the aldol addition and prevents the aldol product epimerising at the α-carbon centre. This should also prevent the sequestration of the Lewis acid by the aldol adduct. Initially, benzaldehyde **12** was chosen as a non-enolisable electrophile. Using these two substrates, various weak bases and several metal ions with differing counter ions were screened. The presence of a ligand and of various additives was examined as well as the effects of changing the solvent and the temperature. This allowed for the optimisation of the conditions for this catalytic reaction.

Once the catalytic conditions were set, the scope of aldehyde substrate was determined, and asymmetric studies were initiated. The need for a rigid transition state required the elaboration of a new bidentate nucleophile for the asymmetric reaction. The screening of various chiral ligands incorporated into the catalytic system and the fine tuning of the catalytic conditions allowed the formation of cyclised aldol products in excellent yield, with good diastereoselectivity and with excellent enantiomeric excess. The early determination of the scope of this catalytic system to various electrophiles is also presented.

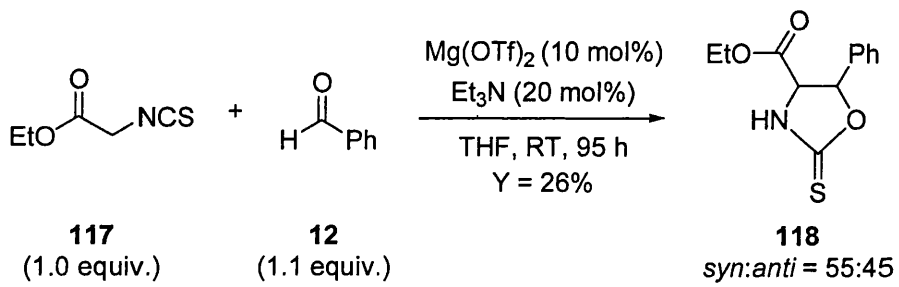
II 2 Soft enolisation and trapping of enolates

II 2A Initial studies

Following the recent report by Ji, Barnes, and co-workers, the first catalyst studied was composed of magnesium trifluoromethanesulfonate (10 mol%) and

triethylamine (20 mol%).[102] After 95 hours at room temperature, under nitrogen, the reaction of ethyl isothiocyanatoacetate **117** (1.0 equiv.) and benzaldehyde **12** (1.1 equiv.) gave the cyclised *syn*- and *anti*-aldol diastereomers (*syn*- and *anti*-5-phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester **118**) in 26% yield, with low diastereoselectivity (*syn*:*anti* = 55:45) (Scheme 39). These two products had spectroscopic data identical to the thioxo-oxazolidines obtained following Hoppe's method.[103,104]

Scheme 39. Ethyl 5-phenyl-2-thioxo-oxazolidine-4-carboxylate.



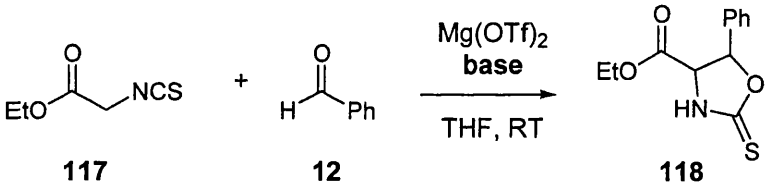
To prove that the pK_a of the proton on the α-carbon to the carbonyl was less acidic than the corresponding protons on the starting material, both diastereomers of oxazolidinethione **118** were subjected to the same catalyst. Pleasingly, after 38 hours at RT no epimerisation was observed. A step-by-step variation of the catalyst was then explored to improve the yield of this reaction.

II 2B Base screening

In an effort to increase the yield of the previous reaction, a few alternative non-nucleophilic bases were tested in this catalytic soft enolisation. These bases have a pK_a in water of approximately 5 to 13.[106] The results for the aldol reaction of

isothiocyanatoacetate **117** and benzaldehyde **12** promoted by $Mg(OTf)_2$ (10 mol%) and these bases (20 mol%) have shown that in addition to TEA (Table 5, entry 5), DABCO was the only effective base to give a reasonable amount of the products (38 % yield after 92 h at RT, entry 3). Bases with a pK_a below 8, for example pyridine and *N*-methylmorpholine, were unable to deprotonate the ester (Entries 1 and 2). Strongly basic amines like DBU and 5,6-dimethylbenzimidazole, with a pK_a above 11, gave lower yields. This might be due to the irreversible formation of a salt of the base and the Lewis acid, which would stop the soft enolisation to occur (Entries 6 and 7). Surprisingly, *N*-ethylpiperidine, which has a pK_a value between those of TEA and DABCO, only gave the aldol products in 9% yield after 45 hours (Entry 4).

Table 5. Soft enolisation using $Mg(OTf)_2$ and various tertiary amine bases.[a]



117 **12** **118**

Entry	Base	pK_a[b]	Time (h)	Yield (%)
1	Pyridine	5.2	50	0
2	*N*-Methylmorpholine	7.4	85	4
3	DABCO	8.8	92	38
4	*N*-Ethylpiperidine	10.5	45	9
5	Triethylamine	10.8	95	26
6	DBU	~12	138	15
7	5,6-dimethylbenzimidazole	12.5	100	5

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(OTf)_2$ (10 mol%) and base (20 mol%).
[b] pK_a in H_2O at RT.[106]

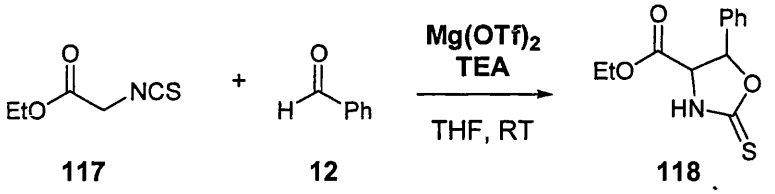
The fact that DABCO was a better base than TEA was not known initially and the screening of non-nucleophilic bases with copper trifluoromethanesulfonate and tin triflate was undertaken. Unfortunately, no enolisation was observed with the copper catalyst in conjunction with any of the bases tested. Low yields were also obtained for $Sn(OTf)_2$ and its use with *N*-methylmorpholine only yielded 3% of the aldol products **118** after 53 hours at RT. The results obtained by soft enolisation with $Mg(OTf)_2$ and TEA or DABCO were encouraging since the yields were greater than the catalyst loading, validating the catalytic hypothesis. However, an improvement of the catalyst turnover was required.

II 2C Different catalyst loadings

In order to understand and increase the catalyst turnover, different catalyst ratios were used. Three experiments with stoichiometric amount of metal salt ($Mg(OTf)_2$) or base (TEA) were conducted and helped to determine the reasons for the low catalyst turnover (Table 6). The reaction with a stoichiometric amount of Lewis acid and only 20 mol% of base gave a slightly higher yield in comparison to the initial results, previously obtained (33% after 76 h, entries 1 and 2). This small increase in yield indicated that the active TEA had been consumed or was not regenerated properly impairing the catalytic cycle. A possibility could be that triethylammonium triflate had difficulties to protonate the magnesium aldolate or cyclised adduct. Similarly, the reaction with only 10 mol% of Lewis acid employed with a stoichiometric amount of base gave the aldol products in 32% yield after 97 hours at RT (Entry 3). This showed that the Lewis acid was somehow trapped by the aldol product, certainly in the same

manner as in the previous reaction, where the ammonium triflate can not protonate the metal aldolate and totally regenerate the Lewis acid for the following catalytic cycle.

Table 6. Different catalyst ratios.[a]



117 12 118

Entry	$Mg(OTf)_2$ (mol%)	TEA (mol%)	Time (h)	Yield (%)
1	10	20	95	26
2	100	20	76	33
3	10	100	97	32
4	110	110	100	66

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.).

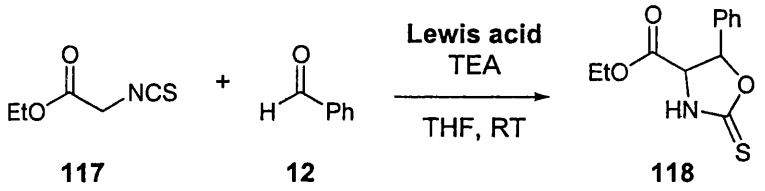
Finally, the reaction with a stoichiometric amount of both the Lewis acid and the base (1.1 equiv. of $Mg(OTf)_2$, and 1.1 equiv. of TEA) was studied and furnished the aldol adducts *syn*- and *anti*-**118** in low yield (66% after 100 h, entry 4). The exact reason for the reaction to stop at a yield of 66% was unclear but could result from aggregation phenomena and difficulties to protonate the aldol adducts. These could prevent access to the remaining unused Lewis acid. Varying the metal centre of the catalyst was the next parameter studied in this reaction.

II 2D Cationic effect

To improve the low catalyst turnover and the low yield of the reaction (26% after 95 h at RT, table 7, entry 1), a few Lewis acids were screened to try to find a more

effective cation than Mg^{2+}. Transition metal cation Sc^{3+} only yielded 5% of the aldol products after 72 hours by reacting ethyl isothiocyanatoacetate **117** and benzaldehyde **12** in THF in presence of catalytic amounts of scandium triflate (10 mol%) and TEA (20 mol%) (Entry 2). Likewise, indium triflate and ytterbium triflate gave the aldol adducts **118** in 5 % yield after 72 hours at RT (Entries 5 and 7). Zinc triflate, similarly to copper and tin triflates previously reported, failed to form any product in combination with TEA (Entries 3, 4 and 6).

Table 7. Effect of the cation in various Lewis acids.[a]



117 **12** **118**

Entry	Lewis acid	Time (h)	Yield (%)
1	$Mg(OTf)_2$	95	26
2	$Sc(OTf)_3$	72	5
3	$Cu(OTf)_2$	63	0
4	$Zn(OTf)_2$	48	0
5	$In(OTf)_3$	72	5
6	$Sn(OTf)_2$	45	0
7	$Yb(OTf)_3$	72	5

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.), Lewis acid (10 mol%) and TEA (20 mol%).

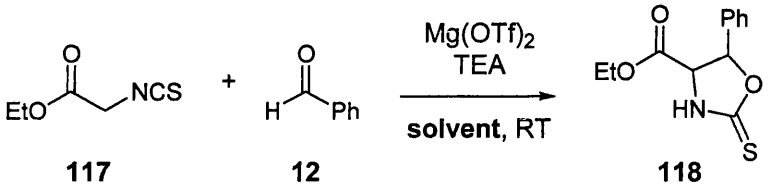
From the few metal salt tested, magnesium triflate gave by far the best results and was kept as the basis of the catalyst and was therefore used in the following determination of the solvent effect on the catalytic cycle.

II 2E Solvent effects

The best catalyst found so far only furnished the aldol adducts in 26% yield after 95 hours at RT in THF (Table 8, entry 5). Changing the solvent of the reaction might reduce the difference of pK_a between ethyl isothiocyanatoacetate coordinated to Mg^{2+} and TEA, increasing the rate of enolisation. It might also accelerate the regeneration of the catalyst. The polarity of the solvent could also have implications on the stabilisation of the transition state or the products, which would influence the rate of the reaction and of the retro aldol reaction. An example of the solvent effect on ethyl isothiocyanatoacetate **117** was analysed by Floch and co-workers.[107] They studied the intramolecular interactions between the carbonyl and the isothiocyanate substituent on the α-carbon to the carbonyl and reported that they were weaker in THF than in chloroform. On the one hand, this might help facilitate the coordination to the catalyst in THF, but on the other hand, it would allow a more facile rotation in the molecule and reduce the selectivity of the enolate formation in THF in comparison to the same reaction in chloroform. Therefore, the effects of several solvents were tested on the aldol addition of ethyl isothiocyanatoacetate **117** and benzaldehyde **12** in the presence of $Mg(OTf)_2$ and TEA under nitrogen, at RT. The reaction in acetonitrile allowed the solubilisation of the Lewis acid but gave a low yield (5% after 85 h, entry 6). This was almost certainly due to the high coordination of the solvent to the magnesium cation, which in turn reduced its Lewis acidity. Less polar solvents like toluene and DCM only gave a 1% yield after 100 hours (Entries 2 and 4). Diethyl ether furnished the aldol adduct in only 7 % yield after 80 hours (Entry 3). Hexane apparently offered the best conditions with a 29 % yield after 100 hours at RT (Entry 1). Nevertheless, a biphasic system was formed and since neither the starting materials nor the products seemed

soluble in hexane, it is more likely that the reaction happened in a concentrated starting materials-products phase rather than in the hexane phase.

Table 8. Solvent screening.[a]



117 **12** **118**

Entry	Solvent	Time (h)	Yield (%)
1	Hexane	100	29
2	Toluene	100	1
3	Ether	80	7
4	DCM	100	1
5	THF	95	26
6	MeCN	85	5

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(OTf)_2$ (10 mol%) and TEA (20 mol%).

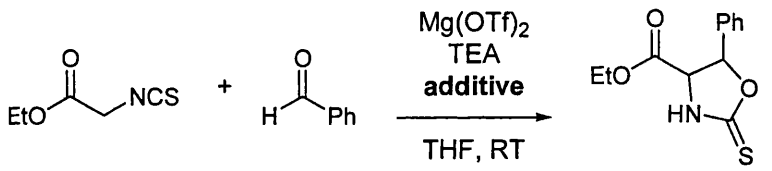
THF was the best solvent for this catalysis and was used in the following attempts to improve the catalyst turnover. Proton sources were thought to protonate the magnesium aldolate and consequently to regenerate the Lewis acid. This was evaluated in the following study.

II 2F Use of additives

The best conditions for the catalytic direct aldol reaction were to employ a Mg^{2+} cation in conjunction with TEA in THF at RT, giving the aldol products *syn*- and *anti*-

118 in 26% yield after 95 hours (Table 9, entry 1). Then stoichiometric amounts of proton sources were employed to hopefully accelerate the regeneration step of the catalyst.[108] Isopropanol failed to improve the turnover of the reaction and gave the aldol adducts in just 14% yield (Entry 2). Similarly, the use of the more acidic and less coordinating 2,2,2-trifluoroethanol only afforded a 16% yield after 71 hours at RT (Entry 3). Another possibility to regenerate the Lewis acid by trapping the newly formed alkoxide was examined. One equivalent of TMS-Cl was added to the reaction media, but after 72 hours at RT no product could be observed by TLC (Entry 4). The TMS-Cl, TEA and $Mg(OTf)_2$, had probably reacted irreversibly and could not generate the aldol product.

Table 9. Proton sources and TMS-Cl.[a]



117 **12** **118**

Entry	Additive	Time (h)	Yield (%)
1	-	95	26
2	^{i}PrOH	71	14
3	CF_3CH_2OH	71	16
4	TMS-Cl	72	0

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(OTf)_2$ (10 mol%), TEA (20 mol%) and additive (1.0 equiv.).

A possible explanation for the non-efficiency of the addition of one equivalent of a proton source is that it might help to regenerate the Lewis acid but not the base. Indeed, the alkoxide might have little effect on the triethylammonium triflate that might

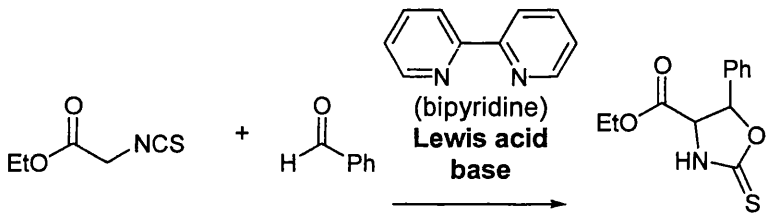
have simply precipitated out of the solution and would therefore be less available. Thus, one part of the catalyst would be missing preventing the soft enolisation from happening. The yields of the reactions employing a proton source were lower than those for the reactions without this proton source. This might be due to the coordination of the proton source to the magnesium cation, reducing its Lewis acidity. The addition of an achiral auxiliary ligand (H_2O, PPh_3S, tetramethylurea)[109] that could hinder the metal centre and enhance the expulsion of the product had not been assessed. However, the use of 10 mol% of a chelate ligand proved to be essential to enhance the yields of the reaction as discussed in the following section.

II 2G Use of 2,6-dipyridyl

The initial conditions for the catalytic aldol reaction of ethyl isothiocyanatoacetate **117** and benzaldehyde **12** (1.1 equiv.) promoted by $Mg(OTf)_2$ (10 mol%) and TEA (20 mol%) in THF at RT had given the best result so far, a 26% yield after 95 hours. However, the need for a chiral ligand that would coordinate the Lewis acid and induce asymmetry in the future asymmetric catalysis was a concern since it could affect the basic activity of the catalyst. Pleasingly, the group of Watanabe had reported an interesting cross aldol addition of α,β-unsaturated ketones that was catalysed by a one to one complex of cobaltous acetate with the non-chiral ligand 2,6-dipyridyl (bipyridine).[110,111] An aldol reaction was then envisaged using a one to one mixture of cobaltous chloride hexahydrate (10 mol%) and bipyridine (10 mol%) in DMF at RT. No product could be observed, even after 67 hours (Table 10, entry 1). Similarly, the use of anhydrous cobaltous chloride and bipyridine failed to furnish any aldol product (Entry 2). However, the reaction catalysed by $CoCl_2$ (10 mol%),

bipyridine (10 mol%) and TEA (20 mol%) in THF gave some aldol product. After 96 hours, the conversion was of 22% (as determined by ^{1}H NMR from the crude after reaction work up) (Entry 3).

Table 10. New screening using bipyridine as a ligand.[a]



117 **12** **118**

Entry	Lewis acid	Base	Solvent	Time (h)	Yield (%)
1	$Co(H_2O)_6Cl_2$	-	DMF	67	0
2	$CoCl_2$	-	DMF	46	0
3	$CoCl_2$	TEA	THF	96	22[b]
4	$Mg(OTf)_2$	-	DMF	141	0
5	$Mg(OTf)_2$	-	THF	94	0
6	$Mg(OTf)_2$	TEA	THF	103	39
7	$Cu(OTf)_2$	-	THF	53	0
8	CuI	TEA	THF	42	11
9	$Sn(OTf)_2$	TEA	THF	100	11
10	$Yb(OTf)_3$	TEA	THF	24	0

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.), Lewis acid (10 mol%), base (20 mol%) and bipyridine (10 mol%).
[b] Conversion determined by ^{1}H NMR.

Since good results had been obtained using a Mg^{2+} cationic centre, two reactions using $Mg(OTf)_2$ were attempted in DMF and in THF following Watanabe's conditions, *i.e.* with one equivalent of bipyridine compared to the metal salt and without TEA (Entries

4 and 5). These reactions failed to deliver any product. Nonetheless, a similar reaction in THF, with TEA (20 mol%) gave the aldol products *syn*- and *anti*-**118** in 39% yield after 103 hours at RT (Entry 6). This was a promising result since the yield had at last increased. Several more reactions were investigated using the same idea of a bipyridine ligand in THF at RT. Copper(II) triflate in the absence of TEA failed to form any product (Entry 7). Ytterbium triflate (10 mol%), bipyridine (10 mol%) and TEA (20 mol%) gave negative results too (Entry 10). Only copper(I) iodide and tin(II) triflate (10 mol%) employed with bipyridine (10 mol%) and TEA (20 mol%) gave positive results, an 11% yield after 42 and 100 hours respectively (Entries 8 and 9).

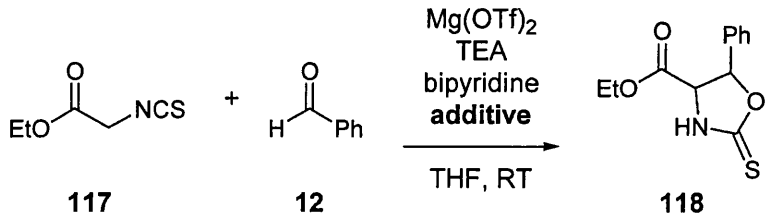
From these data, it also seemed that DMF was not a solvent of choice (Entries 1, 2 and 4) and that TEA was a requisite for the reaction (Entries 1, 2, 4, 5 and 7). Bipyridine which has a pK_a in water at RT of 4.4 was not a base strong enough to promote the soft enolisation of ethyl isothiocyanatoacetate **117** with $Mg(OTf)_2$ (Entry 5 and 6).[106] Furthermore, TEA was shown to play an essential role during the soft enolisation of ethyl isothiocyanatoacetate **117** where $Mg(OTf)_2$ and bipyridine were certainly coordinating to the carbonyl unit and in doing so allowed TEA to deprotonate the α-carbon centre (Entry 5 and 6). Even though additives had not improved the previous reactions catalysed by $Mg(OTf)_2$ and TEA, a second screening of additives was undertaken using the new combination of $Mg(OTf)_2$, bipyridine and TEA in THF at RT. This is presented in the next section.

II 2H Second screening of additives, in combination with bipyridine

The new catalyst for the soft enolisation and the aldol reaction of ethyl isothiocyanatoacetate **117** and benzaldehyde **12** was composed of $Mg(OTf)_2$ (10 mol%),

bipyridine (10 mol%) and TEA (20 mol%). It furnished the aldol adducts in 39% yield after 103 hours in THF at RT. To improve the catalyst turnover, the effects of proton source additives were re-evaluated. The use of one equivalent of isopropanol resulted in an interesting increase of the yield to 50 % after 78 h (Table 11, entry 1). The rate of the reaction appeared to have increased too.

Table 11. New screening of additives.[a]



117 **12** **118**

Entry	Additive	Time (h)	Yield (%)
1	^{i}PrOH	78	50
2	^{i}PrOH	138	53[b]
3	^{i}PrOH	142	25[c]
4	CF_3CH_2OH	94	38
5	$(CF_3)_2CHOH$	75	39
6	H_2O	15	34[d]
7	H_2O + 4 Å MS	142	38[d]

[a] All reactions unless otherwise stated: ester (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(OTf)_2$ (10 mol%), TEA (20 mol%), bipyridine (10 mol%) and additive (1.0 equiv.).
[b] DABCO used instead of TEA.
[c] Hexane use instead of THF as a solvent.
[d] Additive (only 40 mol%).

Using the same additive, but changing the base for DABCO slightly increased the yield but the reaction time was longer (53 % after 138 h, entry 2). A last attempt in hexane, using isopropanol, gave a 25% yield. The low solubility of starting materials and

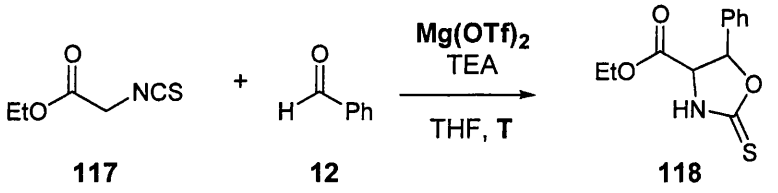
products in this solvent was confirmed (Entry 3). The addition of trifluoroethanol or hexafluoropropan-2-ol gave similar yield to the reaction where no additive was employed (just below 40 %, entries 4 and 5). The reaction times were shorter, 94 h and 75 h respectively, which indicated the positive effect of the proton source in regenerating the catalyst. Water (40 mol%), was also used to form a partially hydrated and more soluble complex with $Mg(OTf)_2$. The aldol products were furnished in 34% yield, after only 15 hours (Entry 6). A similar reaction following the method developed by Ji and Barnes,[102] employing 4 Å MS in addition to the 40 mol% of water gave identical yield but after a much longer reaction time (38 % after 142 h, entry 7).

II 2I Effect of the temperature

In an attempt to accelerate the catalyst turnover of the previous reaction using propan-2-ol, the temperature of the reaction was increased to 50 °C. After 47 hours, the yield of the reaction of ethyl isothiocyanatoacetate **117** with benzaldehyde **12** catalysed by $Mg(OTf)_2$, bipyridine and TEA reached 70 % (Table 12, entry 1). The reaction catalysed without the proton source gave a similar result but required a longer time of reaction (69% yield after 55 hours, entry 2). In absence of propan-2-ol and bipyridine, the reaction was less efficient. The products *syn*- and *anti*-**118** were formed in 63% yield after 75 hours (Entry 3). A major drawback to the reactions catalysed at 50 °C was the non-insignificant base catalysed reaction pathway. Indeed, the reaction catalysed by TEA alone, at various temperatures was studied and revealed that at 50 °C, a yield of 23% was obtained after 94 hours (Entry 4). At room temperature, the same base catalysed reaction was observed and the products were formed in 14% yield after 94 hours (Entry 6). The reaction catalysed in presence of the base and $Mg(OTf)_2$ giving a

slightly higher yield (26%, 95 h, entry 5). Even at 0 °C, the base could catalyse the reaction and furnished the aldol adducts in 18% yield (Entry 7).

Table 12. Effect of the temperature on the catalytic reaction.[a]



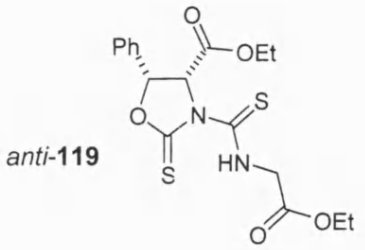
117 **12** **118**

Entry	$Mg(OTf)_2$ (mol%)	T (°C)	Time (h)	Yield (%)
1	10	50	47	70[b,c]
2	10	50	55	69[b]
3	10	50	75	63
4	0	50	94	23
5	10	25	95	26
6	0	25	94	14
7	0	0	49	18

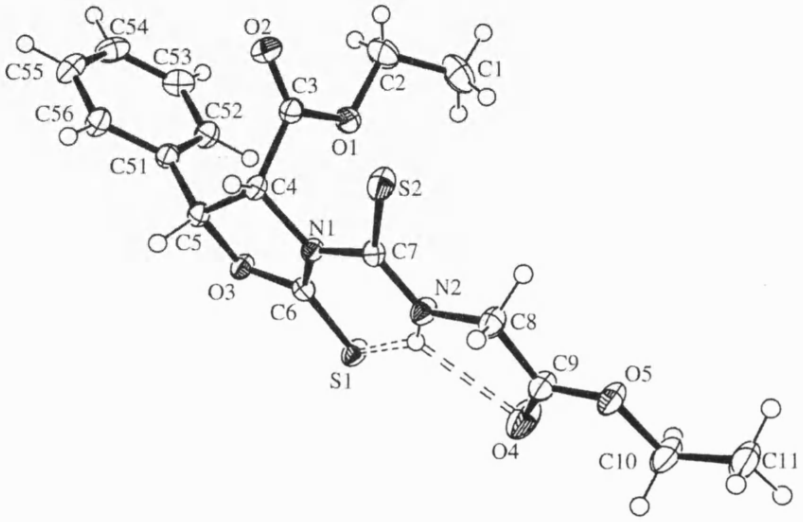
[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.) and TEA (20 mol%).
[b] Use of bipyridine (10 mol%).
[c] Use of ^{i}PrOH (1.0 equiv.).

The drop in yield observed between the reactions catalysed by TEA alone, at 0 °C and at RT was caused by the formation at RT of side products that consumed some of the starting material **117** and adducts **118** (Entries 6 and 7). These side products, *syn*- and *anti*-3-ethoxycarbonylmethylthiocarbamoyl-5-phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester, *syn*- and *anti*-**119,** resulted from the condensation of a molecule of the deprotonated oxazolidinethione adducts **118** with a molecule of ethyl isothiocyanatoacetate **117** (Scheme 40).

Scheme 40. Oxazolidinethione side product *anti*-**119** and X-Ray crystal structure.



anti-**119**



The crystal structure of the side product was required since the connection between the aldol adduct and the starting material at C7 and N1 was not entirely sure. At first, it was thought to result from a bond between the sulphur S1 and the carbon C7. As expected by NMR due to the high coupling constant between 4-H and 5-H (J = 9.1 Hz), the diastereomer observed by X-Ray diffraction was the *anti*-aldol adduct. The molecule is also quite stable since it spent many hours in a mixture of solvents during attempts to grow large crystals.

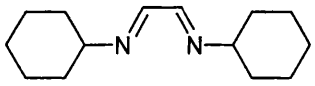
An important fact observed while running these experiments was the synergic effect of using the mild base TEA and the Lewis acid $Mg(OTf)_2$ (Table 12, entries 5 and 6; 3 and 4). The soft enolisation conditions gave much higher yields than the base itself. In the same way, the reaction catalysed by the Lewis acid alone, failed to form any product (*vide supra*, table 10, entry 5). These reactions emphasised that they had to be run at a temperature high enough for the catalyst to be effective but not too high, to minimise as much as possible the base catalysed reaction pathway. The presence of the ligand bipyridine and the proton source showed interesting acceleration of the rate of the reaction. The following reactions were therefore effected at RT and in presence of the bipyridine ligand and a proton source if required. The anionic effect of the Lewis acid counter ion was the last variable evaluated in the discovery of a suitable catalyst for the reaction.

II 2J Counter ion effect

The ultimate attempt to increase the yield of the catalytic aldol reaction came from the variation of the counter ion of the Lewis acid. Along with the use of magnesium halides presented below, magnesium hexafluoroantimonate ($Mg(SbF_6)_2$), supposedly a more dissociated and more soluble salt than $Mg(OTf)_2$, was prepared and used in a few attempts to catalyse the aldol reaction of ethyl isothiocyanatoacetate **117** and benzaldehyde **12** (1.1 equiv.) with TEA (20 mol%) at RT. Several solvents and ligands were used.[112] Generally, magnesium halide (10 mol%), a ligand (10 mol%) and silver hexafluoroantimonate (20 mol%) were stirred for 1 hour at RT in the dark. The mixture was then filtered and the other reactants were added. The reaction catalysed by $Mg(SbF_6)_2$ formed from $MgBr_2$ and bipyridine in THF gave a 12% yield after 160 hours

(Table 13, entry 1). Another reaction with the catalyst prepared from $MgBr_2$, but without the ligand, in ether gave a very low yield (1% after 140 h at RT, entry 2). The same reaction employing a different ligand, *N,N'*-dicyclohexylethanediimine **120** (Scheme 41) in ether resulted in a 5% yield after 120 h (Entry 3).

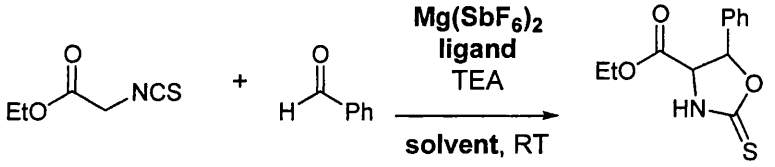
Scheme 41. *N,N'*-Dicyclohexylethanediimine **120**.



120

These low yields obtained by preparing the Lewis acid from $MgBr_2$ where thought to originate from the preparation of the $Mg(SbF_6)_2$.

Table 13. Use of in situ generated $Mg(SbF_6)_2$.[a]



117 **12** **118**

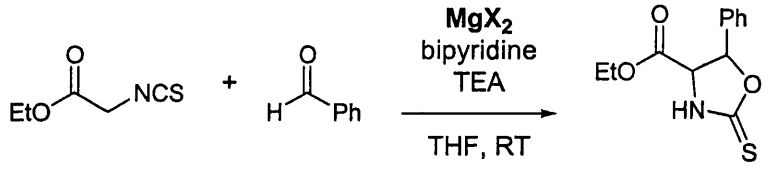
Entry	Initial magnesium salt	Ligand	Solvent	Time (h)	Yield (%)
1	$MgBr_2$	Bipyridine	THF	160	12
2	$MgBr_2$	-	Et_2O	140	1
3	$MgBr_2$	Diimine **120**	Et_2O	120	5
4	$MgCl_2$	Bipyridine	Et_2O	162	0
5	$MgCl_2$	Bipyridine	THF	119	1
6	MgI_2	bipyridine	MeCN/THF	140	8

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(SbF_6)_2$ (10 mol%), ligand (10 mol%) and TEA (20 mol%).

Therefore, two experiments starting with magnesium dichloride were attempted in the presence of bipyridine to help to solubilise $MgCl_2$ and to stabilise the *in situ* generated $Mg(SbF_6)_2$ species. However, both the reaction in ether and the one in THF gave poor results (0% yield after 162 h and 1% after 119 h respectively, entries 4 and 5). Magnesium iodide was soluble in a one to one mixture of acetonitrile and THF and $Mg(SbF_6)_2$ was prepared from MgI_2 with addition of bipyridine in this mixture of solvents. Nonetheless, the adducts were only obtained in 8% yield after 140 hours (Entry 6).

The catalysis promoted by $Mg(SbF_6)_2$ was non-conclusive and the screening of commercially available magnesium salts was evaluated. When $Mg(OTf)_2$ was employed, the yield of the aldol products formed was 39% after 103 h (Table 14, entry 1). $MgCl_2$ gave lower yield (16% after 160 hours, entry 2). Magnesium bromide however gave a much better result with 31% yield after only 15 hours (Entry 3). Magnesium iodide furnished good results too but with a longer reaction time as compared to magnesium bromide (35% yield, 65 h, entry 4). An important improvement observed in using MgI_2 was that no side product formation could be observed. Magnesium nitrate gave similar results to $Mg(OTf)_2$ with a 37% yield after 114 h (Entry 7). The use of a proton source (propan-2-ol) with magnesium iodide failed to improve the rate of the reaction and the aldol adducts were obtained in 37% yield after 69 h (Entry 6). A promising result was obtained when adding to magnesium iodide (10 mol%) the iodine co-catalyst (10 mol%). This was thought to form a less coordinating counter ion I_3^- and improve the Lewis acidity of magnesium.[113] Indeed, the yield and the rate of the reaction were improved (55% after 20 h, entry 5).

Table 14. Effects of the variation of the magnesium(II) counter ion.[a]



117 **12** **118**

Entry	X	Time (h)	Yield (%)
1	OTf^-	103	39
2	Cl^-	160	16
3	Br^-	15	31
4	I^-	65	35
5	I^-	20	55[b]
6	I^-	69	37[c]
7	NO_3^-	114	37
8	ClO_4^-	24	94
9	ClO_4^-	70	19[d]

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.), MgX_2 (10 mol%), bipyridine (10 mol%) and TEA (20 mol%).
[b] I_2 (10 mol%).
[c] ^{i}PrOH (1.0 equiv.).
[d] No bipyridine in this reaction.

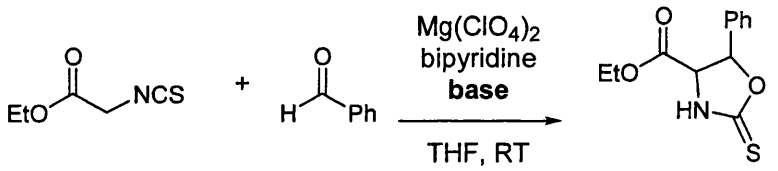
Finally, the success came from anhydrous magnesium perchlorate ($Mg(ClO_4)_2$, 10 mol%). The reaction of ethyl isothiocyanatoacetate **117** (1.0 equiv.) with benzaldehyde **12** (1.1 equiv.) catalysed by $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%) and TEA (20 mol%) formed the adducts *syn*- and *anti*-**118** in 94% yield after only 24 hours (Entry 8). The greater activity of this catalyst was thought to be due to the greater dissociation of the perchlorate counter ion that generated charge separated $[Mg(II)bipyridineClO_4]^+$ species.[114] Importantly, the presence of the ligand was a necessity and the same reaction run without bipyridine only gave a 19% yield after 70 h at RT (Entry 9). This was an

interesting observation since the proposed asymmetric induction was planned to be controlled by the use of a chiral ligand. Before applying this new method to a range of aromatic aldehydes to assess the scope of this reaction, a few small variations of the catalyst and the reaction conditions were tested.

II 2K Optimisation of the $Mg(ClO_4)_2$ containing catalyst

With the efficient $Mg(ClO_4)_2$ based catalyst in hand, a fine tuning of the other components of the catalyst, the solvent and the temperature of the reaction was carried out. The best catalyst for the aldol reaction of ethyl isothiocyanatoacetate **117** and benzaldehyde **12** was composed of $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%) and TEA (20 mol%) in THF at RT for 24 h (94% yield, Table 15, entry 1). Changing the ligand for phenanthroline decreased dramatically the efficiency of the catalyst and gave a conversion of 29% after 45 hours at RT (Entry 2). The change of TEA for the slightly more basic DIPEA lowered the yield of the reaction to 17 % after 40 h (Entry 3). Using DABCO instead of TEA lowered the yield too but only to 58% after 44 h (Entry 4). The use of two slightly more acidic bases than TEA, tri-*normal*-butylamine, and tri-*normal*-propylamine failed to form any product for the former and gave the aldol adducts with a 42% conversion after 23 h for the latter (Entries 9 and 10). A reaction catalysed by $Mg(ClO_4)_2$ and bipyridine only, without using a base formed no product whatsoever after 24 h. This confirmed that the reaction was going through a soft enolisation process (Entry 5). Changing the solvent for DCM only gave a 6% yield after 41 h at RT (Entry 6). This might be due to the poor solubility of the catalyst in this solvent.

Table 15. Fine tuning of the catalyst.[a]



117 **12** **118**

Entry	Base	Time (h)	Yield (%)
1	Et_3N	24	94
2	Et_3N	45	29[b,c]
3	DIPEA	40	17
4	DABCO	44	58
5	-	24	0
6	Et_3N	41	6[d]
7	Et_3N	41	35[c,e]
8	Et_3N	41	23[c,f]
9	$^nBu_3N$	30	0
10	$^nPr_3N$	23	42[c]
11	Et_3N	22	88[g,h]
12	Et_3N	22	2[h,i]
13	Et_3N	21	86[h]

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%) and base (20 mol%).
[b] Bipyridine was replaced by phenanthroline.
[c] Conversion determined by ^1H NMR.
[d] THF was replaced by DCM.
[e] Base (10 mol%).
[f] Reaction conditions twice as dilute as usually.
[g] Aldehyde (2 equiv.).
[h] T = 0 °C.
[i] THF was replaced by EtOAc.

Employing only 10 mol% of TEA impaired the reaction and the observed conversion was 35% after 41 h at RT (Entry 7). Diluting the reaction by two had the same result and the conversion was 23 % after 41 h (Entry 8). All of these small changes had been fruitless, but knowing that the side-reaction pathway due to catalysis by the base alone would be detrimental to an efficient asymmetric induction, the temperature of the reaction was lowered to 0 °C. Two equivalents of aldehyde were employed instead of 1.1, hopping to displace the equilibrium in favour of the products (Entry 11). The yield of the reaction was then 88% after 22 h. When THF was replaced by a more coordinating solvent EtOAc that helped to dissolve the catalyst, the yield of the reaction at 0 °C with benzaldehyde **12** (1.1 equiv.) was only of 2% after 22 h (Entry 12). The coordination of the solvent was certainly competing too much with ethyl isothiocyanatoacetate **117**, sequestrating the magnesium cation. Nevertheless, the optimal conditions for the aldol reaction of ethyl isothiocyanatoacetate **117** (1.0 equiv.) with only 1.1 equivalents of benzaldehyde **12** were observed using a catalyst formed with $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%) and TEA (20 mol%) in THF. The adducts *syn*- and *anti*-**118** were formed in 86% yield after 21 h at 0 °C (Entry 13). These conditions were then used to study the range of aromatic aldehydes that would undergo the reaction.

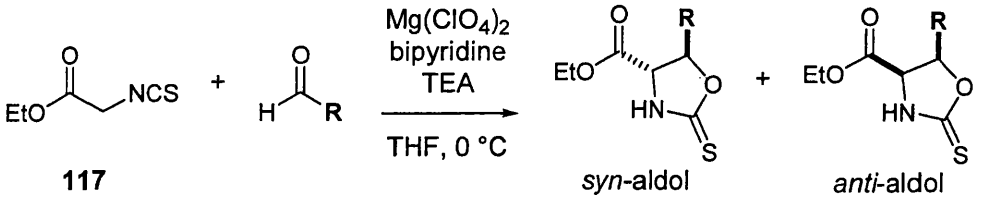
II 3 Variation in aldehyde component

With optimised conditions in hand, the scope of this catalytic aldol reaction was extended to various aromatic aldehydes. The different positions of the substitution on the phenyl ring were investigated as well as the electron donating or electron withdrawing ability of the substituents. To reduce the formation of side product **119** and

the enolisation by TEA itself, the temperature of the reaction was lowered to 0 °C. At this temperature, the reaction of ethyl isothiocyanatoacetate **117** (1.0 equiv.) with benzaldehyde **12** (1.1 equiv.) furnished the *syn*- and *anti*-aldol adducts **118** in 86% yield after 21 hours, in favour of the *syn*-isomer (*syn*:*anti* = 65:35, table 16, entry 1). Electron poor aldehydes such as *para*-nitrobenzaldehyde and *para*-cyanobenzaldehyde gave good yields too, 70% after 25 h for **121** and 85% after 22 h for **122** respectively (Entries 2 and 3). In comparison to the non-substituted benzaldehyde, slightly higher selectivities for the *syn*-aldol products were obtained (*syn*:*anti* = 70:30 and 75:25 respectively). For the electron withdrawing bromobenzaldehydes, similar results were obtained and the position of the substituent had little effect on the yields and the diastereomeric selectivity. *Ortho*-bromobenzaldehyde furnished the aldol adduct **123** in 84% yield after 23 hours (*syn*:*anti* = 65:35, entry 4). *Meta*-bromobenzaldehyde gave the same selectivity but with a higher yield of adduct **124** (88% after 21 h, entry 5). After 21 hours, *para*-bromobenzaldehyde formed the oxazolidinethione **125** in 84% yield and good *syn*-selectivity (*syn*:*anti* = 70:30, entry 6). Pleasingly, the sterically hindered 2,6-dichlorobenzaldehyde gave the oxazolidinethione **126** with a reasonable yield (49%, 25 h, entry 7) and a good *syn*-selectivity (*syn*:*anti* = 70:30). Electron rich aldehydes such as *para*-anisaldehyde gave the cyclised aldol products **127** in moderate yield (67%, 23 h, entry 8) and low selectivity (*syn*:*anti* = 60:40). Despite the same low *syn*-selectivity, 2-naphthaldehyde, an electron rich aldehyde, gave an excellent yield for the *syn*- and *anti*-adducts **128** (89%, 21 h, entry 9). Several of these reactions had to be carefully repeated in order to obtain consistent yields. This was due to the susceptibility of the catalyst to any perturbation like traces of water or other impurities that could complex the Lewis acid. One more aromatic aldehyde was tested, *para*-*N*,*N*-dimethylaminobenzaldehyde (Entry 10). The ^{1}H-NMR of the crude mixture was promising and a good conversion of

around 85% was observed due to the presence of two couples of doublets in the 4-H and 5-H shift region of the NMR spectrum. However, the products could not be separated from the remaining starting materials or purified by silica or alumina column chromatography. The attempt to promote the combination of ethyl isothiocyanatoacetate **117** (1.0 equiv.) and the dihydrocinnamaldehyde (1.1 equiv.) under the same catalytic conditions failed to form any product after 24 h (Entry 11).

Table 16. Screening of aromatic aldehydes.[a]



117 *syn*-aldol *anti*-aldol

Entry	R	Product	Time (h)	*Syn:Anti*[b]	Yield (%)[c]
1	C_6H_5	**118**	21	65:35	86
2	4-NO_2-C_6H_4	**121**	25	70:30	70
3	4-CN-C_6H_4	**122**	22	75:25	85
4	2-Br-C_6H_4	**123**	23	65:35	84
5	3-Br-C_6H_4	**124**	21	65:35	88
6	4-Br-C_6H_4	**125**	21	70:30	84
7	2,6-diCl-C_6H_3	**126**	25	70:30	49
8	4-OMe-C_6H_4	**127**	23	60:40	67
9	2-naphthyl	**128**	21	60:40	89
10	4-(Me_2N)-C_6H_4	-	24	-	89[d]
11	C_6H_5-CH_2-CH_2	-	24	-	0

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.).
[b] Determined by ^{1}H NMR.
[c] Combined yield of the isolated diastereomers.
[d] Conversion determined by ^{1}H NMR.

Despite these two last unsuccessful attempts, the method proved to be general for the catalysis of the aldol addition and cyclisation of the commercially available ethyl isothiocyanatoacetate **117** with a range of aromatic aldehydes. The reactivity toward less electrophilic aldehydes was expected to be higher than for more electrophilic aldehydes that would have more difficulties to coordinate the Lewis acid.[115] However, the products were all obtained in good yields and with moderate diastereoselectivity. The need for a ligand to form an active catalyst was encouraging for the following part of the project and the asymmetric induction was studied by replacing the bipyridine with various chiral ligands.

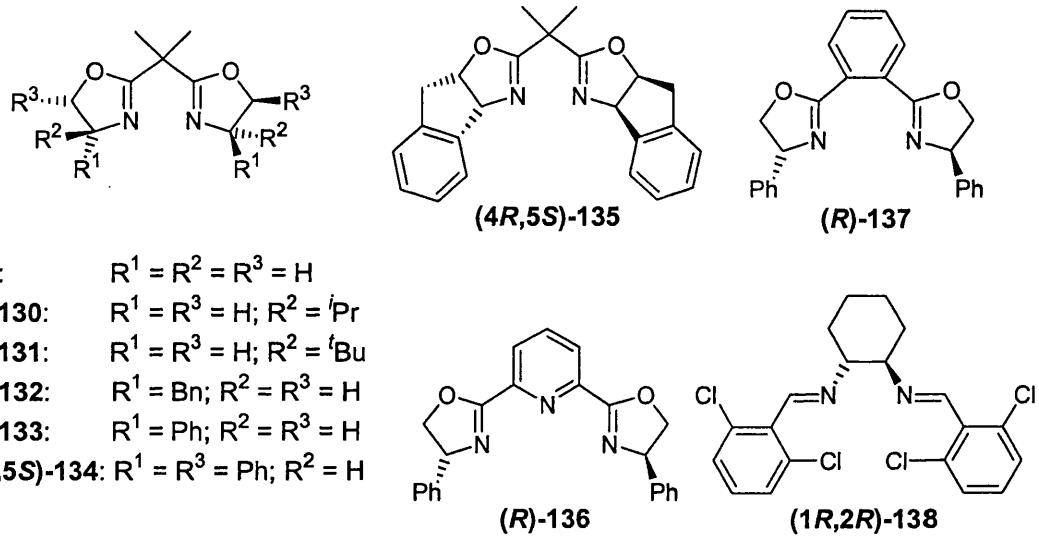
II 4 Asymmetric induction with ethyl isothiocyanatoacetate

The catalyst composed of $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%) and TEA (20 mol%) gave excellent results for the aldol reaction of ethyl isothiocyanatoacetate **117** with a range of aromatic aldehydes. The reaction at 0 °C with benzaldehyde **12** (1.1 equiv.) furnished after 21 h the products in 86% yield, and a *syn*:*anti* ratio of 65:35 (Table 17, entry 1). Chiral bipyridines were not commercially available and the few synthetic routes already reported were long.[116,117,118] Chiral bisoxazolines have been widely used in asymmetric synthesis.[119] Their easy access, either commercially available or readily synthesised, made them attractive ligands for this asymmetric catalysis (Appendix C). Following the typical procedure (Section III 2) $Mg(ClO_4)_2$ (10 mol%) and the ligand (10 mol%) were stirred for 10 minutes at RT in THF, then TEA (20 mol%) was added and the temperature was lowered to 0 °C. After 15 minutes, ethyl isothiocyanatoacetate **117** (1.0 equiv.) and benzaldehyde **12** (1.1 equiv.) were added. The reaction progress was followed by TLC and stopped as in the

typical method. Unlike previously, where the magnesium cation was involved in a six-membered ring complex with the bipyridine ligand, with most bisoxazoline ligands, the Lewis acid was incorporated in a five-membered chelate. The first reaction used the unsubstituted bisoxazoline **129** (BOx, scheme 42) to ensure the good activity of the catalyst with this type of ligand. This ligand was synthesised using the methodology developed by Witte and Seeliger (Section III 2).[120] The yield of the reaction after 19 hours at 0 °C was lower than with bipyridine but was still reasonably high (84%, entry 2). The *syn*-selectivity had also dropped (*syn*:*anti* = 55:45). The first asymmetric reaction employed the (*S*)-isopropylbisoxazoline (*S*)-**130** ((*S*)-^{i}PrBOx). The yield of the reaction was of 60%, no diastereoselectivity was observed and the enantiomeric excess determined by chiral HPLC, was nearly non-existent (ee_{syn}:ee_{anti} = 5%:4%, entry 3). Evans *et al.* successfully employed in a copper(II) catalysed asymmetric Diels-Alder reaction the more hindered (*S*)-*tert*-butylbisoxazoline (*S*)-**131** ((*S*)-^{t}BuBOx).[121] With this ligand, after 23 hours, the diastereomeric selectivity was back in favour of the *syn*-isomer but the ee's were low (*syn*:*anti* = 55:45, ee_{syn}:ee_{anti} = 3%:0%, entry 4). The yield was again lower than the achiral version of the catalysis (74%). The benzyl-substituted bisoxazoline (*R*)-**132** ((*R*)-BnBOx) furnished the highest enantioselectivity and *syn*-selectivity (ee_{syn}:ee_{anti} = 12%:18%, *syn*:*anti* = 60:40, entry 5). However, this was at the expense of a low yield (8% after 24 h). The more hindered ligand, phenylbisoxazoline (*R*)-**133** ((*R*)-PhBOx), gave excellent results in Corey's iron(III) enantioselective Diels-Alder addition.[112] Desimoni *et al.* also used this ligand for an asymmetric Diels-Alder reaction catalysed by $Mg(ClO_4)_2$.[122] However, this chiral ligand failed to improve the selectivity of the present reaction (ee_{syn}:ee_{anti} = 2%:10%, *syn*:*anti* = 55:45, entry 6) and after 24 h, the yield was only 26%. The *cis*-diphenylbisoxazoline (4*R*,5*S*)-**134** ((4*R*,5*S*)-diPhBOx), supposedly having a more rigid geometry gave the aldol adducts in higher

yield (65% after 21 h, entry 7). Nevertheless, the selectivity of the reaction remained low (ee_{syn}:ee_{anti} = 6%:2%, *syn*:*anti* = 55:45). A second more rigid ligand, the indane bisoxazoline (4*R*,5*S*)-**135** ((4*R*,5*S*)-indBOx) was efficiently used by Davies and co-workers in a Diels-Alder reaction but proved to be of little help in this reaction since the yield, the diastereoselectivity and the enantioselectivity were all smaller than for diPhBOx (Y = 52%, *syn*:*anti* = 55:45 and ee_{syn}:ee_{anti} = 1%:3%, entry 8).[123]

Scheme 42. Ligands screened during the asymmetric catalysis.

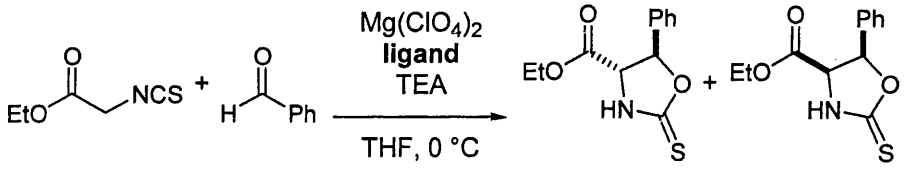


129: $R^1 = R^2 = R^3 = H$
(*S*)-130: $R^1 = R^3 = H$; $R^2 = {}^{i}Pr$
(*S*)-131: $R^1 = R^3 = H$; $R^2 = {}^{t}Bu$
(*R*)-132: $R^1 = Bn$; $R^2 = R^3 = H$
(*R*)-133: $R^1 = Ph$; $R^2 = R^3 = H$
(4*R*,5*S*)-134: $R^1 = R^3 = Ph$; $R^2 = H$

Then, two different types of bridging unit were employed in the ligand. The first one, the tridentate bisoxazoline-substituted pyridine (*R*)-**136** ((*R*)-PhPyBOx), was initially used by Nishiyama *et al.* for the enantioselective hydrosilylation of ketones with Rh.[36] This ligand furnished a good selectivity (*syn*:*anti* = 70:30, entry 9), but the yield and enantiomeric excess were far too low (9% yield after 20 h, ee_{syn}:ee_{anti} = 3%:1%). The second ligand, the 1,2-disubstituted benzene (*R*)-**137** ((*R*)-PhBenzBOx), was employed in combination with magnesium iodide in an enantioselective Claisen rearrangement.[124,125] This ligand formed a seven-membered ring with Mg^{2+} and

furnished the products in reasonable yields (54% after 22 h, entry 10) but without selectivity (*syn*:*anti* = 50:50, ee_{syn}:ee_{anti} = 1%:0%).

Table 17. Screening of chiral ligand.[a]



117 **12** *syn*-**118** *anti*-**118**

Entry	Ligand	Time (h)	*Syn*:*anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	bipyridine	21	65:35	-	86
2	BOx	19	55:45	-	82
3	(*S*)-^{i}PrBOx	19	50:50	5:4	60
4	(*S*)-^{t}BuBOx	23	55:45	3:0	74
5	(*R*)-BnBOx	24	60:40	12:18	8
6	(*R*)-PhBOx	24	55:45	2:10	26
7	(4*R*,5*S*)-diPhBOx	21	55:45	6:2	65
8	(4*R*,5*S*)-indBOx	23	55:45	1:3	52
9	(*R*)-PhPyBOx	20	70:30	3:1	9
10	(*R*)-PhBenzBOx	22	50:50	1:0	54
11	(*trans*)-^{c}Hexanediimine	24	50:50	6:1	34

[a] All reactions: ester (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), TEA (20 mol%) and ligand (10 mol%).
[b] Diastereomeric ratio determined by ^{1}H NMR.
[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.

Then a different type of chiral ligand was used. The *trans*-diimine (1*R*,2*R*)-**138** first reported by Jacobsen *et al.* in an asymmetric alkene aziridination, was readily synthesised from the chiral 1,2-diaminocyclohexane and the bulky

dichlorobenzaldehyde.[126] Like bipyridine, the ligand formed a five-membered ring with the Lewis acid. However, the yield and selectivity were low (34% after 24 h, *syn:anti* = 50:50, ee_{syn}:ee_{anti} = 6%:1%, entry 11).

The reaction with the non-substituted bisoxazoline **129** gave a reasonable yield, which implied that the low yields observed using the chiral bisoxazolines came from the steric hindrance of the magnesium Lewis acid provoked by the substituents. The cation became less active either at the enolisation step or at the activation of the benzaldehyde, when coordinating to the electrophile. The poor selectivity of the reaction could come from a low binding affinity of the ligands to magnesium perchlorate. Once the enolate was formed, the steric repulsions might force the ligand to leave and allow the binding of the electrophile and its activation. The tridentate nature of PhPyBOx could therefore explain the higher diastereoselectivity obtained. The best enantiomeric excess was observed when using BnBOx **125**. This was explained by the increased length of the benzyl substituents on the ligand, creating a deeper chiral pocket and reaching the actual bond formation area. Most likely, the main problem of this asymmetric attempt came from the ester ethyl isothiocyanatoacetate **117** and its inability to generate a rigid transition state. Therefore, the synthesis of a bidentate imide was investigated as this would provide a rigid transition state.

II 5 Two-point binding enolate

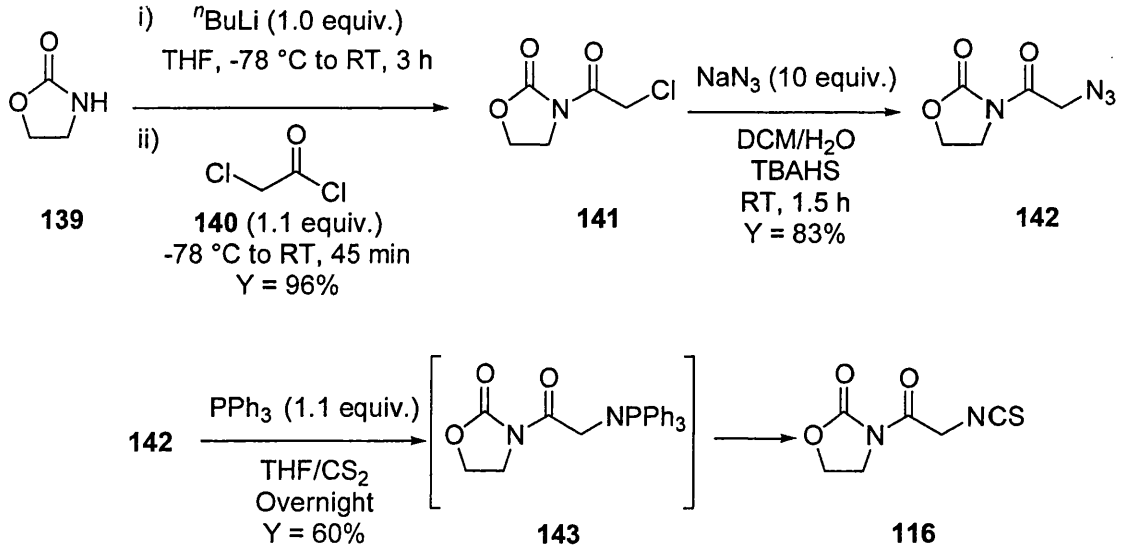
The attempt to generate enantiomerically enriched chiral oxazolidinethiones from the ester ethyl isothiocyanatoacetate **117** had failed and delivered 18% ee in the best case. A more rigid transition state was thought to be required. The addition of an Evans's type non-chiral chelating oxazolidinone auxiliary to the starting material was

proposed to solve this problem.[88] The synthesis of the new starting material is presented in the following section. Then, using magnesium perchlorate as the Lewis acid, variation of different parameters such as the temperature, the base, the solvent system and the chiral ligand was investigated and is detailed in the following sections.

II 5A Chelating substrate synthesis

Following the procedure for the synthesis of chiral isothiocyanatoacetyl-oxazolidinone reported by Evans *et al.*, the non-chiral 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one **116** (OxNCSAc) was synthesised (Scheme 43).[10]

Scheme 43. 3-(2-Isothiocyanatoacetyl)-oxazolidin-2-one **116**.



To circumvent the difficulties due to low solubility of oxazolidin-2-one **139**, larger amounts of solvent were used (Section III 3). After addition of ^{n}BuLi (1.0 equiv.) at -78 °C, the temperature was increased to room temperature for two and a half hours. Chloroacetyl chloride **140** (1.1 equiv.) was added dropwise to this suspension at -78 °C.

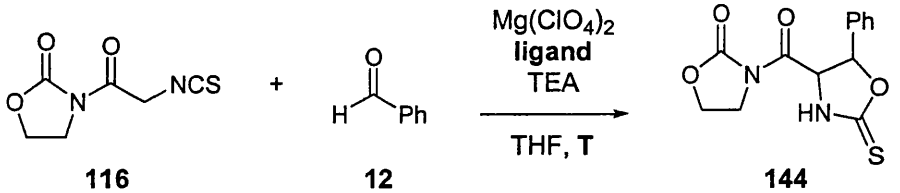
The chloroimide **141** was isolated in 96% yield and formed after nucleophilic substitution the azidoimide **142** in 83% yield. Triphenylphosphoazoimide **143** was formed *in situ* by reaction of triphenylphosphine (1.1 equiv.) with a solution of the azidoimide **142** in THF and carbon disulfide. The phosphazoimide **143** reacted with carbon disulfide to form the isothiocyanatoimide **116** in 60% yield.

II 5B Preliminary results

With this new starting material OxNCSAc **116** in hand, further asymmetric catalysis was investigated. The initial catalyst was composed of $Mg(ClO_4)_2$ (10 mol%), the non-chiral bipyridine (10 mol%) and TEA (20 mol%). This was first tested to check the reactivity with the substrate **116**. The reaction at 0 °C gave a full conversion to the products **144** after 3 hours (Table 18, entry 1). A few minutes after starting the reaction, the products were already precipitating in the reaction vessel. The reaction rate had been exceptionally enhanced but a major drawback appeared; the reaction catalysed by TEA (20 mol%) alone gave a 53% conversion after 2 hours at 0 °C (Entry 2). Therefore, in order to shut or at least lower this non-chiral reaction pathway, the temperature of the following reactions was lowered to -78 °C. The reaction with $Mg(ClO_4)_2$, bipyridine and TEA, conducted at -78 °C furnished the products in 94% conversion after 2 hours (Entry 3). No determination of the background reaction catalysed by the base alone at -78 °C was effected at this stage but it was later found to be rather high while using DIPEA alone, in dilute conditions, with 4 Å MS (Y = 39% after 22 h at -78 °C, table 28, entry 13). Then the chiral ligand (*S*)-^{t}BuBOx (*S*)-**131** was used at -78 °C in combination with $Mg(ClO_4)_2$ and TEA. After 2 h, the conversion was 42%. This was lower than when the ester **117** was used, but could be due to premature quenching of the reaction.

The two diastereomers **144** were purified by column chromatography and then analysed by chiral HPLC but were too polar to determine any enantiomeric excess (*vide infra*). A similar reaction that omitted TEA failed to form any product even after prolonged exposure at -78 °C (Entry 5). The mild base was therefore essential to promote the catalysis.

Table 18. Initial results using the chelating starting material.[a]



116 **12** **144**

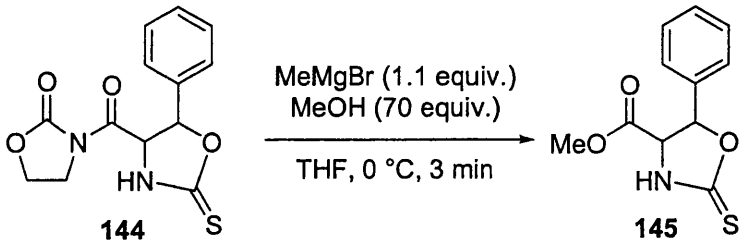
Entry	Ligand	T (°C)	Time (h)	Conversion (%)[b]
1	bipyridine	0	3	100
2	-	0	2	53[c]
3	bipyridine	-78	2	94
4	(*S*)-^{t}BuBOx	-78	2	42
5	(*S*)-^{t}BuBOx	-78	20	0[d]

[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), TEA (20 mol%) and ligand (10 mol%).
[b] Conversion determined by ^{1}H NMR.
[c] No Lewis acid in the reaction media.
[d] No TEA used in this reaction.

It remained to determine the asymmetric induction generated by the use of the new starting material and the chiral ligand (*S*)-^{t}BuBOx (*S*)-**131**. The products with the auxiliary were very polar and had incredibly high retention times (from 56 min to more than 160 min). Evans *et al.* reported a method for the removal of chiral oxazolidinone auxiliaries forming methyl esters.[10] Since the ethyl esters **118** were easily separable analytically by chiral HPLC, the methyl esters equivalents should allow the

determination of the enantiomeric excesses. Due to the low solubility of the oxazolidinethione **144**, the methanolysis promoted by MeMgBr (1.1 equiv.) in methanol (70 equiv.) and THF had to be run in more dilute conditions than reported (Scheme 44).

Scheme 44. Methanolysis of the imide **144**.



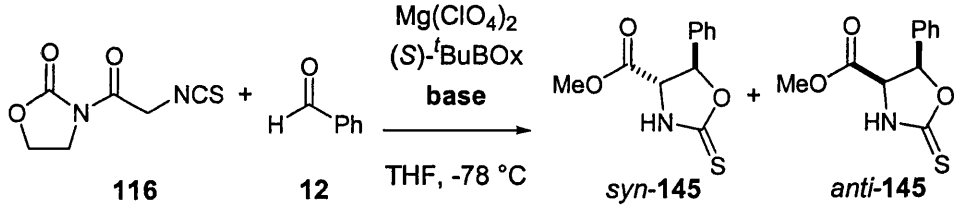
After 3 minutes at 0 °C, no epimerisation at the α-carbon centre was observed with both the *syn*- and *anti*-oxazolidinethiones **144**. When a diastereomericaly pure *syn*-**144** was subjected to methanolysis conditions, *syn*-**145** was formed in 67% without any trace of *anti*-**145**. Similarly, when a mixture of *syn*- and *anti*-**144** (*syn*:*anti* = 81:19) was subjected to methanolysis, a close ratio of the diastereomers *syn*- and *anti*-**145** was obtained (67% yield, *syn*:*anti* = 82:18). The HPLC analysis of the methyl ester adducts formed using (*S*)-^{t}BuBOx (*S*)-**131** indicated a low enantiomeric induction (ee_{syn}:ee_{anti} = 3%:8%). In the following section, an attempt to improve this enantiomeric selectivity by screening different mild bases is reported.

II 5C Base screening using the chelating substrate

The first results obtained with OxNCSAc **116** in the catalysis with (*S*)-^{t}BuBOx (*S*)-**131** furnished a low yield, 42% after 2 h and a low selectivity (*syn*:*anti* = 55:45, ee_{syn}:ee_{anti} = 3%:8%, table 19, entry 1). The slightly stronger base DIPEA was next used

instead of TEA and gave a better yield (71% after 3 h, entry 2), a good diastereoselectivity (*syn*:*anti* = 90:10) but a low enantioselectivity (ee_{syn}:ee_{anti} = 2%:12%). In an attempt to stop the racemic reaction pathway catalysed by the base alone, milder bases that would effect a more selective reaction were screened. Bases with pK_a lower than TEA ranging between 5 to 10 were employed, commencing with $^nBu_3N$. After 1 h at -78 °C, the reaction yielded 65% of the products *syn*- and *anti*-adducts **145** with a good *syn*-selectivity (*syn*:*anti* = 90:10, entry 3). No asymmetric induction was observed (ee_{syn}:ee_{anti} = 2%:3%). Using DABCO as a base, furnished similar results and after 2 h at -78 °C, the adducts **145** were formed in 67% yield with as reasonable *syn*-selectivity (*syn*:*anti* = 75:25, entry 4) but no sign of improvement of the enantioselectivity was noticed (ee_{syn}:ee_{anti} = 4%:0%). The much milder base NMM (pK_a order 3 times lower than TEA in water at 25 °C) still yielded the *syn*- and *anti*-aldol adducts **145** in 59% after 3 h, with a good *syn*-selectivity (*syn*:*anti* = 80:20, entry 5). However, no enantioselectivity could be detected (ee_{syn}:ee_{anti} = 2%:2%). NMIm was a too mild base and only furnished the adducts in 38% yield after extended reaction time (21 h at -78 °C, entry 6). The diastereoselectivity was good (*syn*:*anti* = 70:30) but no ee improvement was observed (ee_{syn}:ee_{anti} = 4%:1%). Then diethylaniline and dimethylaniline were used. After 20 h at -78 °C, no reaction had happened and the temperature was allowed to warm to 0 °C for a further 28 hours. Diethylaniline gave a good *syn*-diastereoselectivity (*syn*:*anti* = 90:10, entry 7) but the yield and the ee's were rather low (yield = 30%, ee_{syn}:ee_{anti} = 10%:4%). Dimethylaniline furnished the adducts with a higher yield (48%, entry 8) but the selectivity was lower (*syn*:*anti* = 75:25, ee_{syn}:ee_{anti} = 7%:9%).

Table 19. Base screening.[a]



Entry	Base	Time (h)	*Syn:anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	TEA	2	55:45	3:8	42
2	DIPEA	3	90:10	2:12	71
3	$^{n}Bu_3N$	1	75:25	2:3	65
4	DABCO	2	75:25	4:0	67
5	NMM	3	80:20	2:2	59
6	NMIm	21	70:30	4:1	38
7	Et_2PhN	48[d]	90:10	10:4	30
8	Me_2PhN	48[d]	75:25	7:9	42

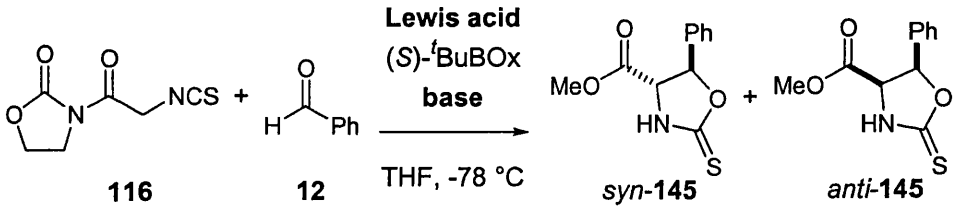
[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), base (20 mol%) and (*S*)-^{t}BuBOx (10 mol%).
[b] Diastereomeric ratio determined by ^{1}H NMR.
[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.
[d] 20 h at -78 °C then 28 h at 0 °C.

None of the reactions employing the chelating auxiliary had reached the 18% enantiomeric excess observed earlier (Section II 4, table 17, entry 5). The ee's with (*S*)-^{t}BuBOx were nevertheless higher than for the reaction using the ester **117** as starting material. DIPEA, having the highest yield and selectivity for this reaction, seemed to be the base of choice for the following investigation. Small variations of the catalytic conditions were subsequently evaluated.

Two reactions included a 20 hours premix phase of the Lewis acid ($Mg(ClO_4)_2$, 10 mol%) and the ligand ((*S*)-^{t}BuBOx, 10 mol%) at room temperature in THF. Nevertheless, the first reaction was less efficient with only 37% yield after 6 h (*syn:anti*

= 70:30, ee_{syn}:ee_{anti} = 2%:6%, table 20, entry 1). This low yield was thought to be caused by the trapping of traces of water by the hygroscopic $Mg(ClO_4)_2$. Consequently, the second premix comprised 4 Å MS. The yield was still low (37% after 6 h, entry 2) and the diastereoselectivity had dropped (*syn*:*anti* = 65:35), but the ee's had slightly improved (ee_{syn}:ee_{anti} = 3%:14%).

Table 20. Various modifications using (*S*)-^{t}BuBOx and DIPEA.[a]



116 12 *syn*-145 *anti*-145

Entry	Lewis acid	Base	Time (h)	*Syn*:*anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	$Mg(ClO_4)_2$	DIPEA	6	70:30	2:6	37[d]
2	$Mg(ClO_4)_2$	DIPEA	6	65:35	3:14	37[d,e]
3	$Mg(OTf)_2$	TEA	21	60:40	7:14	26
4	$Sn(OTf)_2$	NEP	22	95:5	13:29	14

[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), Lewis acid (10 mol%), base (20 mol%) and (*S*)-^{t}BuBOx (10 mol%).
[b] Diastereomeric ratio determined by ^{1}H NMR.
[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.
[d] Lewis acid and (*S*)-^{t}BuBOx were premixed for 20 hours at RT.
[e] Addition of 4 Å MS.

To ensure that no mistake was made in choosing $Mg(ClO_4)_2$ as the Lewis acid, a reaction using $Mg(OTf)_2$ (10 mol%) was performed. Combined with the use of (*S*)-^{t}BuBOx (10 mol%) and TEA (20 mol%), after 21 h, a much longer time than for the perchlorate salt, the products were only formed in a 26% yield (Entry 3). The selectivity of this reaction was as low as with $Mg(ClO_4)_2$ (*syn*:*anti* = 60:40, ee_{syn}:ee_{anti} = 7%:14%). The original stoichiometric reaction developed by the Evans group, employed $Sn(OTf)_2$

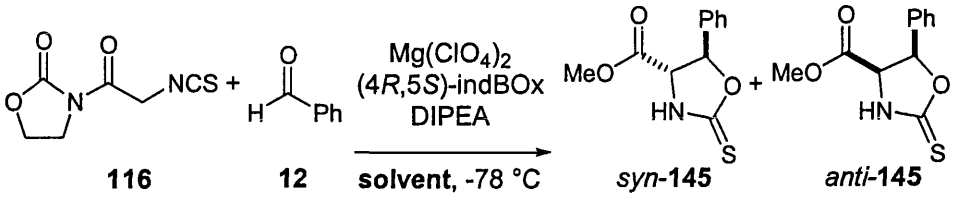
and *N*-ethylpiperidine.[10] Using this same catalytic combination of Lewis acid and mild base, with (*S*)-^{t}BuBOx (10 mol%) only gave 14% yield after 22 h at -78 °C (Entry 4). The diastereoselectivity was excellent, favouring the *syn*-aldol adduct (*syn*:*anti* = 95:5) and for the first time the enantiomeric excess surpassed the 18% ee of the reaction with the ethyl ester (ee_{syn}:ee_{anti} = 13%:29%). Blocked by low yields, long reaction times and low asymmetric inductions, another ligand that had been prepared on a gram scale, (4*R*,5*S*)-IndBOx, was next used to screen different solvents in combination with $Mg(ClO_4)_2$ and DIPEA.

II 5D Solvent screening

Changing the ligand (*S*)-^{t}BuBOx for (4*R*,5*S*)-indBOx (4*R*,5*R*)-**135** (10 mol%) in the reaction catalysed by $Mg(ClO_4)_2$ (10 mol%) and DIPEA (20 mol%) improved the yield of the reaction to 89 % after 2 h (Table 21, entry 1) (compared to 71% yield, 3h, *syn*:*anti* = 90:10, ee_{syn}:ee_{anti} = 2%:12%, table 19, entry 2). The combined yield of the aldol adducts after methanolysis had been improved, which meant that the methanolysis conditions had been improved. The reaction was still highly *syn*-selective (*syn*:*anti* = 90:10), but the ee's were low (ee_{syn}:ee_{anti} = 1%:16%). A test reaction employing $Mg(ClO_4)_2$ (10 mol%) and TEA (20 mol%) was carried out in the absence of a ligand. After 15 minutes the reaction seemed to have gone to completion and delivered the aldol adducts in 62% yield (*syn*:*anti* = 75:25, entry 2). This reaction highlighted an important side-reaction pathway that furnished a racemic mixture and was probably quicker than the reaction employing a ligand. Therefore, unlike the catalytic aldol reaction of ester **117**, that required the use of a bipyridine ligand, the minimal amount of

insoluble $Mg(ClO_4)_2$, non coordinated by a chiral ligand, could potentially become a catalyst toward the racemic reaction.

Table 21. Solvent screening at the concentration of 0.25 mol.L^{-1}.[a]



116 **12** *syn*-**145** *anti*-**145**

Entry	Solvent	Time (h)	*Syn*:*anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	THF	2	90:10	1:16	89
2	THF	1/4	75:25	-	62[d]
3	$CHCl_3$	3	80:20	10:35	46
4	DCM	5	80:20	37:38	56

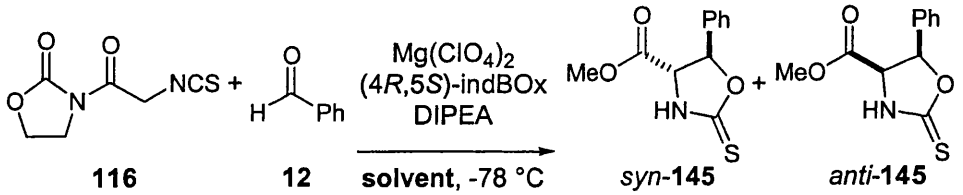
[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and (4*R*,5*S*)-indBOx (10 mol%).
[b] Diastereomeric ratio determined by ^{1}H NMR.
[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.
[d] No ligand was used and DIPEA was replaced by TEA.

The majority of the reactions appeared to be heterogeneous and the low enantioselectivities may have resulted from the aforementioned side-reaction. In an attempt to discover better conditions for the solubility of the Lewis acid, in presence of the ligand, the solvent was changed to chloroform. After 3 hours, at -78 °C, the adducts *syn*- and *anti*-**145** were obtained in 46% yield (Entry 3). This was a poorer result than previously reported in THF but the diastereoselectivity was good (*syn*:*anti* = 80:20) and for the first time the reaction with $Mg(ClO_4)_2$, had at last improved to a 35% ee (ee_{syn}:ee_{anti} = 10%:35%). The reaction was next run in DCM and the yield was slightly improved (56% yield after 5 h, entry 4). The diastereoselectivity was the same as for the

reaction in chloroform but both diastereomers had an improved enantiomeric excess (ee_{syn}:ee_{anti} = 37%:38%).

In view of the enhancement of enantioselectivity by changing the solvent conditions, the concentration of the initial starting material OxNCSAc **116** was divided by five to reach 0.05 mol.L^{-1}. Using the same catalyst as used in the previous set of data, the reaction in dry THF at -78 °C was stopped prematurely forming the *syn*-aldols adducts **145** in 25% yield after 6 h with a 23% ee (Table 22, Entry 1). No *anti*-diastereomer was observed.

Table 22. Solvent screening with dilute conditions (0.05 mol.L^{-1}).[a]



116 **12** **solvent**, -78 °C *syn*-**145** *anti*-**145**

Entry	Solvent	Time (h)	*Syn*:*anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	THF	5	100:0	23:-	25
2	DCM	26	80:20	40:50	69
3	MeCN[d]	16	75:25	5:3	27
4	EtCN	20	90:10	34:7	51
5	EtOAc	22	-	-	0
6	EtOH	22	70:30	4:5	16
7	DMF	19	80:20	6:0	60
8	Toluene[e]	20	70:30	17:8	10

[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and (4*R*,5*S*)-indBOx (10 mol%).

[b] Diastereomeric ratio determined by ^{1}H NMR.

[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.

[d] T was increased to RT.

[e] Preparation of the catalyst by refluxing one hour $Mg(ClO_4)_2$ and (4*R*,5*S*)-indBOx in toluene.

An identical reaction in DCM gave a diastereomeric mixture (*syn*:*anti* = 80:20) of aldol adducts in 69% yield after 26 hours at -78 °C (Entry 2). The asymmetric induction had finally reached 50% enantiomeric excess for the *anti*-diastereomer ***anti*-145** and 40% for the *syn*-isomer ***syn*-145**. Subsequent reactions were run in a number of more solvating solvents in an attempt to eliminate any uncomplexed $Mg(ClO_4)_2$ species. The first was carried out in acetonitrile and the temperature was increased to room temperature. However, the yield of the reaction was poor (27% after 16 h, entry 3). The reaction was *syn*-selective (*syn*:*anti* = 75:25) but the enantiomeric excess was nearly non-existent (ee_{syn}:ee_{anti} = 5%:3%). A second reaction was carried out in propionitrile allowing the temperature to be decreased and maintained at -78 °C. After 20 hours, the yield of formed adduct was 51% with a preference for the *syn*-aldol adduct (*syn*:*anti* = 90:10, entry 4). Nevertheless, the ee's were low (ee_{syn}:ee_{anti} = 34%:7%). A reaction was carried out in EtOAc with the hope that the chelating substrate **116** would gain access to the Lewis acid but as for the ester **117**, no product was formed (Entry 5). Magnesium perchlorate was known to be soluble in ethanol, however after 22 h in this solvent, the reaction only furnished 16% of the adducts with low enantioselectivity (*syn*:*anti* = 70:30, ee_{syn}:ee_{anti} = 4%:5%, entry 6). Surprisingly, the reaction carried out in DMF gave the adducts in reasonable yield (60% after 19 h, entry 7). The low ee's obtained for this reaction tends to indicate the complete dissociation of the ion pair metal-enolate, generating an active non-chiral enolate. A final attempt to change the solvent was inspired by the excellent yield and selectivity of a Diels-Alder reaction catalysed by Mg^{2+}, reported by the group of Yamauchi.[127] Their catalyst was obtained by refluxing a magnesium salt in the presence of a PhBOx ligand in acetonitrile for 3 hours. Concerned by our previous low results obtained in CH_3CN, the catalyst was preformed in refluxing toluene for 1 h prior to the addition of OxNCSAc **116** at RT. Nevertheless,

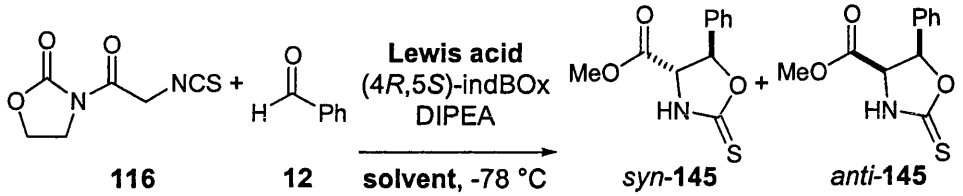
after 20 h at -78 °C, only 10% of the products were formed (Entry 8). The diastereoselectivity was still *syn*-selective (*syn*:*anti* = 70:30) but despite this, the ee's were low (ee_{syn}:ee_{anti} = 17%:8%). The best result from this series of reactions was obtained in DCM, delivering both adducts with moderate enantioselectivity. Therefore, a few more reactions utilising (4*R*,5*S*)-indBOx and magnesium(II) were performed in DCM and are reported in the following section.

II 5E Variations around the Lewis acid

After the fruitless reaction that included the preparation of the catalyst by refluxing in toluene, a second attempt was undertaken to pre-form the catalyst by refluxing $Mg(ClO_4)_2$ and (4*R*,5*S*)-indBOx for 3 h in DCM. Unfortunately, the ee's were lower than expected (ee_{syn}:ee_{anti} = 20%:28%, table 23, entry 1) even so, the yield and the diastereoselectivity were good (59% yield after 19 h, *syn*:*anti* = 75:25). Another attempt to improve the solubility of the Lewis acid by allowing its complexation with the chiral ligand (4*R*,5*S*)-indBOx employed acetonitrile as an additive. At first, six equivalents relative to the metal Mg^{2+} were used but the salt proved insoluble. Therefore, more acetonitrile was added and the salt eventually dissolved by employing a large excess of acetonitrile (1 mL, 120 equiv.). The yield of the reaction had decreased to 46% after 22 h at -78 °C and although the diastereoselectivity was still reasonable (*syn*:*anti* = 75:25, entry 2), no asymmetric induction was observed (ee_{syn}:ee_{anti} = 4%:0%). Then, $[Mg(H_2O)_6](ClO_4)_2$, which was soluble in THF, was used in two reactions. In DCM, the salt was not very soluble and after 26 h, the yield of aldol adducts was only 26%, with no selectivity (*syn*:*anti* = 50:50, ee_{syn}:ee_{anti} = 1%:0%, entry 3). In THF, the yield and

diastereoselectivity were slightly better (31% yield after 26 h, *syn*:*anti* = 75:25, entry 4) but the enantiomeric excesses were similar (ee_{syn}:ee_{anti} = 0%:2%).

Table 23. Further attempts to form an active catalyst.[a]



116 **12** ***syn*-145** ***anti*-145**

Entry	Lewis acid	Solvent	Time (h)	*Syn*:*anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	$Mg(ClO_4)_2$	DCM	19	75:25	20:28	59[d]
2	$Mg(ClO_4)_2$	DCM	22	75:25	4:0	46[e]
3	$Mg(H_2O)_6(ClO_4)_2$	DCM	26	50:50	1:0	26
4	$Mg(H_2O)_6(ClO_4)_2$	THF	26	75:25	0:2	31
5	$MgI_2 + I_2$	DCM	28	90:10	1:3	36[f]
6	$Mg(SbF_6)_2$	DCM	34	-	-	0
7	$Mg(SbF_6)_2$	DCM	34	50:50	13:1	50[g]
8	$Mg(SbF_6)_2$	EtCN	24	75:25	20:7	3[g]

[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), Lewis acid (10 mol%), DIPEA (20 mol%) and (4*R*,5*S*)-indBOx (10 mol%).
[b] Diastereomeric ratio determined by ^1H NMR.
[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.
[d] Preparation of the catalyst by refluxing $Mg(ClO_4)_2$ and (4*R*,5*S*)-indBOx in DCM for three hours.
[e] Addition of 1 mL of MeCN.
[f] T was increased to RT.
[g] Filtration of the catalyst.

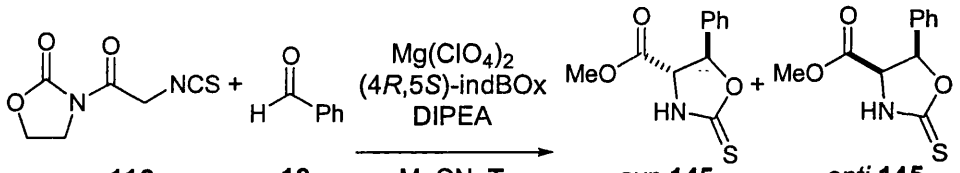
Finally, different counter-ions that should form more dissociated species, were used (I_3^- and SbF_6^-). The first reaction employed MgI_2 and 10 mol% of the co-catalyst iodine as described by Corey and recently by Yamauchi.[112,128] Nonetheless, the reaction had to be warmed to room temperature because no product could be seen after several hours and

furnished the aldol adducts in 36% yield after 28 h (Entry 5). The diastereoselectivity was very good (*syn*:*anti* = 90:10), but no enantiomeric excess was observed (ee_{syn}:ee_{anti} = 1%:3%). With regards to the reaction employing $Mg(SbF_6)_2$ in DCM, no filtration of the AgCl was performed, so as to avoid removal of the active catalyst. Disappointingly, no product was formed even with prolonged reaction time (Entry 6). When the catalyst was filtered through a dry frit-glass funnel, the products *syn*- and *anti*-oxazolidinethione **145** were obtained in 50% yield after 34 h at -78 °C (Entry 7). No diastereoselectivity was detected and the enantioselectivity was poor (ee_{syn}:ee_{anti} = 13%:1%). The same reaction in propionitrile, after filtration, gave a low yield of adduct (3% after 24 h, entry 8), with some selectivity being observed (*syn*:*anti* = 75:25, ee_{syn}:ee_{anti} = 20%:7%).

No improvement had emerged from this fine-tuning of the catalytic conditions. Having noticed that the Lewis acid was soluble in acetonitrile, a few more reactions with this solvent were attempted. Both the concentration and the temperature of the reaction were varied. At the initial concentration of 0.25 $mol.L^{-1}$ in acetonitrile, the reaction of OxNCSAc **116** and benzaldehyde **12** (1.1 equiv.) catalysed by $Mg(ClO_4)_2$ (10 mol%), (4*R*,5*S*)-indBOx (4*R*,5*S*)-**135** (10 mol%) and DIPEA (20 mol%) at 0 °C for 7 h yielded the adducts *syn*- and *anti*-**145** in 43% (*syn*:*anti* = 75:25, table 24, entry 1). The enantiomeric excess of the *syn*-diastereomer was the highest ever observed (ee_{syn}:ee_{anti} = 63%:10%). The reaction was then attempted in dilute conditions (0.05 $mol.L^{-1}$). The reaction started at -45 °C and was allowed to warm to room temperature since no product formation could be observed. After 30 h, the aldol adducts were formed in 16% yield in good diastereoselectivity (*syn*:*anti* = 80:20, entry 2). Nevertheless, the enantioselectivity was much lower than in the more concentrated conditions (ee_{syn}:ee_{anti} = 29%:3%). A second reaction in dilute conditions was attempted, this time, the catalyst was prepared in the presence of the chelating starting

material **116**, to help the solubilisation of the Lewis acid. The reaction was much quicker and after 6 h, the products were formed in 58% (Entry 3). The diastereoselectivity was excellent (*syn*:*anti* = 95:5) but the enantioselectivity was again low (ee_{syn}:ee_{anti} = 9%:15%). Finally, a reaction in acetonitrile that started at room temperature furnished the adducts in 77% yield after only 7 h (*syn*:*anti* = 90:10, entry 4). However, the enantioselectivity was again limited (ee_{syn}:ee_{anti} = 48%:10%).

Table 24. Use of acetonitrile as solvent.[a]



116 **12** *syn*-**145** *anti*-**145**

Entry	Concentration (mol.L^{-1})	T (°C)	Time (h)	*Syn*:*anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	1/4	0	7	75:25	63:10	43
2	1/20	-45 to RT	30	80:20	29:3	16
3	1/20	-45 to RT	6	95:5	9:15	58[d]
4	1/20	RT	7	90:10	48:10	77

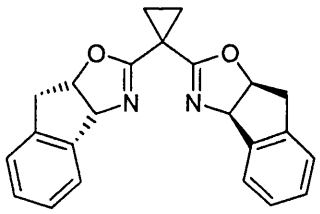
[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and (4*R*,5*S*)-indBOx (10 mol%).
[b] Diastereomeric ratio determined by ^1H NMR.
[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.
[d] Substrate **116** added first with the ligand and the Lewis acid catalyst.

Although some improvements were observed when using acetonitrile, they were irregular and the yield of the reaction which gave an interesting ee was low. Therefore, a screening of the chiral ligand in dilute conditions in DCM at -78 °C was performed and is presented in the following section.

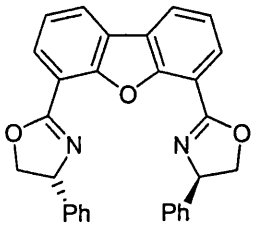
II 5F Chiral ligand screening

The enantioselectivity of the reactions that employed the ligands (*S*)-^{t}BuBOx and (4*R*,5*S*)-indBOx could not be increased as high as necessary. The use of the ligand (4*R*,5*S*)-indBOx in combination with $Mg(ClO_4)_2$ and DIPEA in DCM furnished an encouraging 69% yield, after 26 h at -78 °C, with a reasonable selectivity (*syn*:*anti* = 90:10, ee_{syn}:ee_{anti} = 40%:50%, table 25, entry 1). Using the same conditions, several more chiral ligands were screened in an attempt to improve the stereoselectivity of the reaction (Scheme 45).

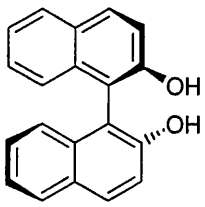
Scheme 45. New chiral ligands used in the screening.



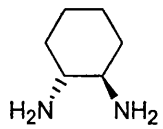
(4*R*,5*S*)-146



(*R*)-147



(*R*)-148



(1*R*,2*R*)-149

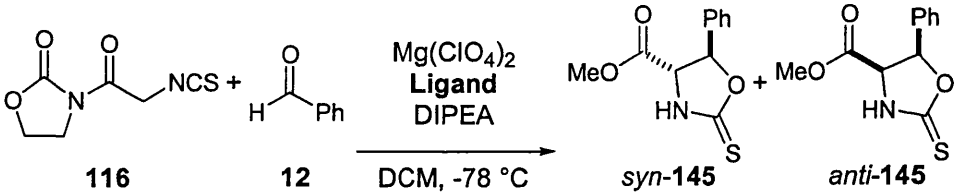
The cyclopropyl-indane-bisoxazoline (4*R*,5*S*)-**146** ((4*R*,5*S*)-^{c}propylindBOx) was first reported by Sibi *et al.* and used in an efficient enantioselective synthesis of *β*-amino acid precursors.[128] This ligand also possesses a greater bite angle in comparison to the previous indBOx **135**. This larger angle was correlated by the Davies group to a greater selectivity of the resultant catalyst in Diels-Alder reactions.[129] However, after 20 h, the

yield and selectivity of the reaction were disappointing (36% yield, *syn*:*anti* = 60:40, ee_{syn}:ee_{anti} = 5%:18%, entry 2). The reaction with the less constricted (*R*)-PhBOx (*R*)-**133** furnished low results too (30% yield after 22 h, *syn*:*anti* = 55:45, ee_{syn}:ee_{anti} = 12%:2%, entry 3). The ligand (*R*)-BnBOx (*R*)-**132** that gave the best enantioselectivity when using the ester **117** gave lower results when using the imide **116** (43% yield after 24 h, *syn*:*anti* = 55:45, ee_{syn}:ee_{anti} = 13%:5%, entry 4). The result using (*S*)-^{t}BuBOx (*S*)-**131**, in dilute conditions this time, failed to improve the enantioselectivity and the yield was poorer (65% yield after 24 h, *syn*:*anti* = 65:35, ee_{syn}:ee_{anti} = 7%:0%, entry 5). The tridentate phenyl substituted dibenzofuran bisoxazoline (*R*)-**147**, (*R*)-PhDBFOx, was then used, hoping that this tridentate ligand would completely dissolve $Mg(ClO_4)_2$. This ligand had successfully been used by Kanemasa *et al.* in combination with $Mg(ClO_4)_2$ and $Ni(ClO_4)_2$ in water-tolerant Diels-Alder and Michael reactions.[130,131,132] Unfortunately, low selectivity was observed (52% yield after 19 h, *syn*:*anti* = 50:50, ee_{syn}:ee_{anti} = 16%:5%, entry 6). The synthesis of indane-substituted DBFOx was attempted but proved problematic. Following the reported methodology for the synthesis of (*R*)-**147**, (2*R*)-2-amino-2-phenylethanol was changed for 1-aminoindanol but the cyclised ligand could not be formed. The tridentate ligand (*R*)-PhPyBOx (*R*)-**136**, that had failed to furnish any enantioselectivity with the ester **117**, delivered exceptional results. After 16 h at -78 °C, the adducts *syn*- and *anti*-**145** were formed in 76% yield with a good diastereoselectivity (*syn*:*anti* = 80:20, entry 7) and very good enantioselectivity (ee_{syn}:ee_{anti} = 76%:75%).

An attempt to use the chiral *trans*-diimine (1*R*,2*R*)-**138** gave a low yield (24% after 23 h, entry 8). The diastereoselectivity was reversed and favoured the *anti*-aldol diastereomer (*syn*:*anti* = 40:60). These low yield and unusual *anti*-selectivity in this reaction may be due to the extremely bulky nature of the chiral ligand. However, the

enantioselectivity was low and nearly non-existent for the *anti*-isomer (ee_{syn}:ee_{anti} = 17%:2%). $Mg(ClO_4)_2$ is soluble in various amines and in alcohols, as these molecules have the ability to coordinate to the magnesium cation and in turn solubilise it. The formation of crystals of magnesium complexed with amines has also been reported.[133] Consequently, two chiral diamines were employed.

Table 25. New screening of chiral ligands.[a]



116 **12** *syn*-**145** *anti*-**145**

Entry	Ligand	Time (h)	*Syn*:*anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	(4*R*,5*S*)-indBOx	26	80:20	40:50	69
2	(4*R*,5*S*)-^{c}propylindBOx	20	60:40	5:18	36
3	(*R*)-PhBOx	22	55:45	12:2	30
4	(*R*)-BnBOx	24	55:45	13:5	43
5	(*S*)-^{t}BuBOx	24	65:35	7:0	65
6	(*R*)-PhDBFOx	19	50:50	16:5	52
7	(*R*)-PhPyBOx	16	80:20	76:75	76
8	(*R*,*R*)-^{c}Hexanediimine	23	40:60	17:2	24
9	(-)-Sparteine	20	85:15	55:45	73[d]
10	(*R*)-(+)-BINOL	16	60:40	6:1	51
11	(*R*,*R*)-^{c}Hexanediamine	16	60:40	18:1	49

[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and ligand (10 mol%). The initial concentration of imide in solution was 1/20 mol.L^{-1}.

[b] Diastereomeric ratio determined by ^{1}H NMR.

[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.

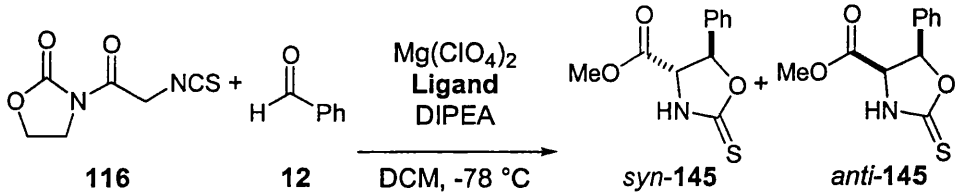
[d] DIPEA was replaced by adding 10 mol% more of (-)-sparteine.

The first, 1,2-diaminocyclohexane (1*R*,2*R*)-**149**, gave the adducts in low yield (49% after 16 h, entry 11) with little selectivity (*syn*:*anti* = 60:40, ee_{syn}:ee_{anti} = 18%:1%). Nevertheless, when (-)-sparteine **107**, which creates a deeper chiral pocket, was employed as a ligand and as a base replacing DIPEA, good results were obtained (73% yield after 20 h, *syn*:*anti* = 85:15, ee_{syn}:ee_{anti} = 55%:45%, entry 9). The diol, (*R*)-BINOL (*R*)-**148**, gave a reasonable yield (51% after 16 h, entry 10) but the selectivity of the reaction was low (*syn*:*anti* = 60:40, ee_{syn}:ee_{anti} = 6%:1%). Good results were obtained while using PhPyBOx (*R*)-**136**, but problems arose due to the difficulty to reproduce the selectivity of the reaction described in entry 7. A detailed investigation into the order of addition of the catalyst components and the imide **116** solved the problem and is presented below.

Since $Mg(ClO_4)_2$ was reported to dissolve in amine bases, it was thought that the 20 mol% of DIPEA used for the soft enolisation could help to dissolve the Lewis acid into the DCM by coordination of the cation. This would facilitate the complexation by the chiral ligand of the non-coordinated salt. When using (4*R*,5*S*)-indBOx (4*R*,5*S*)-**135**, $Mg(ClO_4)_2$ and the chiral ligand were first mixed together in dry DCM at RT then the base was added and the stirring was continued. The temperature was lowered to -78 °C and the starting materials were added. The good yield of the reaction (69% after 26 h, table 26, entry 1) and the selectivity were encouraging (*syn*:*anti* = 80:20, ee_{syn}:ee_{anti} = 40%:50%). In a second reaction, all of the substrate **116** was added at the same time as the ligand and the Lewis acid to enhance the complexation of the cation. It was only when the temperature had reached -78 °C that the base was added. The yield of the formed *syn*- and *anti*-adducts **145** decreased slightly (61% after 20 h, entry 2), however, the loss of stereoselectivity was dramatic (*syn*:*anti* = 65:35, ee_{syn}:ee_{anti} = 2%:8%). Another attempt to form the active catalyst used only 10 mol% of the substrate **116** at

the beginning. The temperature was then lowered to -78 °C, and then the base and the remaining substrate were added. Like the previous attempt, despite a good diastereoselectivity, the yield and enantioselectivity were low (59% after 20 h, *syn:anti* = 90:10, ee_{syn}:ee_{anti} = 13%:18%, entry 3).

Table 26. Difference in the order of addition of the base and of the imide.[a]



116 **12** *syn*-**145** *anti*-**145**

Entry	Ligand	Conditions	Time (h)	*Syn:anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	(4*R*,5*S*)-indBOx	Base first	26	80:20	40:50	69
2	(4*R*,5*S*)-indBOx	Substrate first[d]	20	65:35	2:8	61
3	(4*R*,5*S*)-indBOx	Substrate first[e]	20	90:10	13:18	59
4	(4*R*,5*S*)-indBOx	Substrate first[e,f]	17	65:35	11:6	56
5	(*R*)-PhDBFOx	Base first	19	55:45	16:5	52
6	(*R*)-PhDBFOx	Substrate first[d]	21	65:35	12:1	59
7	(*R*)-PhPyBOx	Base first	20	65:35	47:28	59
8	(*R*)-PhPyBOx	Substrate first[d]	16	80:20	76:75	76
9	(*R*)-PhPyBOx	Substrate first[e]	20	75:25	84:71	61

[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and ligand (10 mol%). The initial concentration of imide in solution was 1/20 $mol.L^{-1}$.

[b] Diastereomeric ratio determined by ^1H NMR.

[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.

[d] 100 mol%.

[e] 10 mol%.

[f] Filtration of the catalyst.

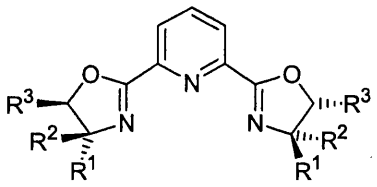
A separate attempt to remove the supposed non-complexed or non-solubilised $Mg(ClO_4)_2$ by filtration after preparation of the catalyst with addition of 10 mol% of the substrate **116** from the beginning, failed and furnished similar results as previously reported (56% after 17 h, *syn*:*anti* = 65:35, ee_{syn}:ee_{anti} = 11%:6%, entry 4). The order of addition of the reactants for the catalysis using indBOx as a ligand was essential to get enhanced enantioselectivity; the base had to be added prior to the imide. However, when using (*R*)-PhDBFOx (*R*)-**147,** adding the base DIPEA before the substrate **116**, or the other way round, had little effect on the result of the catalysis. Indeed, when the base was added first, after 19 h at -78 °C, the *syn*- and *anti*-adducts **145** were formed in 52% yield, with low selectivity (*syn*:*anti* = 55:45, ee_{syn}:ee_{anti} = 16%:5%, entry 5). In the reaction where the substrate **116** was added before the base, DIPEA, the yield was slightly higher but the selectivity was low too (59% after 21 h, *syn*:*anti* = 65:35, ee_{syn}:ee_{anti} = 12%:1%, entry 6). However, with the tridentate ligand (*R*)-PhPyBOx (*R*)-**136** the order of addition was altered. When the base was added after the imide **116**, at -78 °C, the reaction gave good results (76% after 16 h, *syn*:*anti* = 80:20, ee_{syn}:ee_{anti} = 76%:75%, entry 8). The enantioselectivity could also be improved to 84% for the *syn*-enantiomers, by adding only 10 mol% of the imide at the beginning. This resulted in a small loss of yield and diastereoselectivity (61% after 20 h, *syn*:*anti* = 75:25, ee_{syn}:ee_{anti} = 84%:71%, entry 9). The addition of the base prior to the addition of the substrate **116**, was detrimental to the enantioselectivity since the best ee observed was 47% (59% yield after 20 h, *syn*:*anti* = 65:35, ee_{syn}:ee_{anti} = 47%:28%, entry 7). With a deeper chiral pocket in comparison to other usual bis oxazolines, PhPyBOx had finally delivered a high level of asymmetric induction. The catalyst had to be prepared by premixing the Lewis acid, the ligand and the starting material; the base being added when the

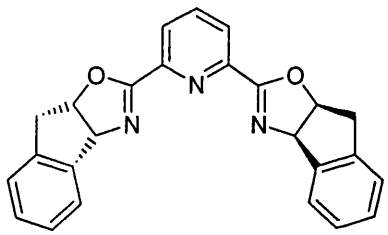
temperature had reached -78 °C. With these conditions in hand, the effect of various substituents on the oxazoline ring of the PyBOx ligand was investigated.

II 5G Variation of substituent on PyBOx ligand

The PhPyBOx ligand **136** transferred a good asymmetric induction to the newly generated aldol adducts. Therefore, in an attempt to improve this asymmetric induction, commercially available chiral PyBOx and more constricted PyBOx ligands were gathered and assessed on this asymmetric aldol reaction (Scheme 46) (Appendix C). To ensure the complexation of every molecule of magnesium perchlorate, a slight excess of ligand was employed (11 mol%).

Scheme 46. Various PyBOx ligands employed for the following screening.





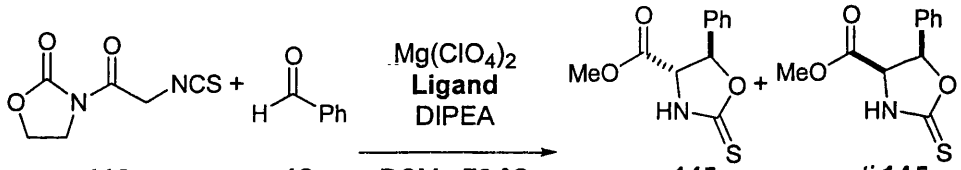
(*R*)-136: R^1 = Ph; R^2 = R^3 = H
(*S*)-150: R^1 = R^3 = H; R^2 = ^{t}Bu
(*S*)-151: R^1 = R^3 = H; R^2 = Bn
(4*R*,5*R*)-152: R^1 = Me; R^2 = H; R^3 = Ph
(4*R*,5*R*)-153: R^1 = R^3 = Ph; R^2 = H

(4*R*,5*S*)-154

Repeating the previous reaction with (*R*)-PhPyBOx (11 mol%), by adding all of substrate **116** at the beginning, furnished a slightly smaller yield and diastereoselectivity but the enantioselectivity was improved (71% after 20 h, *syn*:*anti* = 75:25, ee_{syn}:ee_{anti} = 83%:68%, table 27, entry 1). When only 10 mol% of the substrate **116** was added at the beginning, the same order of selectivity was obtained. Since adding all the substrate in

one batch was easier than adding at two different stages, and since the results were similar, all following reactions were prepared by adding all of the imide with the ligand. The more rigid indane substituted pyridine bisoxazoline (4*R*,5*S*)-**154** ((4*R*,5*S*)-indPyBOx) was prepared and used in the asymmetric catalysis.[134] The yield remained high but unfortunately, the selectivity of the reaction had dropped (70% after 21 h, *syn*:*anti* = 60:40, ee_{syn}:ee_{anti} = 67%:40%, entry 2).

Table 27. PyBOx screening.[a]



116 **12** *syn*-**145** *anti*-**145**

Entry	Ligand	Time (h)	*Syn*:*anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	(*R*)-PhPyBOx	20	75:25	83:68	71
2	(4*R*,5*S*)-indPyBOx	21	60:40	67:40	70
3	(4*R*,5*S*)-diPhPyBOx	18	90:10	73:56	69
4	(*S*)-BnPyBOx	22	70:30	45:15	53
5	(4*R*,5*R*)-4-Me-5-PhPyBOx	19	80:20	55:21	71
6	(*S*)-^{t}BuPyBOx	21	35:65	8:44	51

[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and ligand (11 mol%). The initial concentration of imide in solution was 1/20 mol.L^{-1}. The substrate **116** was added first.

[b] Diastereomeric ratio determined by ^1H NMR.

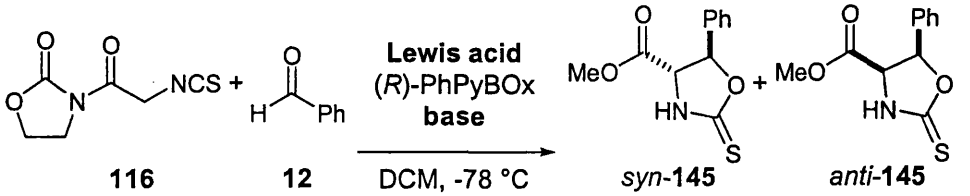
[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.

The *trans*-diphenyl substituted pyridine bisoxazoline (4*R*,5*R*)-**153** ((4*R*,5*R*)-diPhPyBOx) was also obtained. Following Desimoni's procedures and the modifications he kindly provided, the ligand still had to be purified by column chromatography and was identical to the analytical sample they had provided.[135]

Desimoni *et al.* had obtained excellent results in an enantioselective *exo*-Diels-Alder reaction.[136] However, the results of the catalytic aldol reaction were not up to expectations and despite the good yield and diastereoselectivity (69% after 18 h, *syn*:*anti* = 90:10, entry 3), the enantioselectivity of the *syn*- and *anti*-aldol adducts **145** was below the selectivity obtained with PhPyBOx (ee_{syn}:ee_{anti} = 73%:56%). Three more PyBOx type ligands were employed but failed to deliver improved enantioselectivities. The benzyl substituted pyridine bisoxazoline (*S*)-**151** ((*S*)-BnPyBOx) may have furnished good selectivity due to its deep chiral pocket, but in fact, the yield and selectivity were seriously eroded (53% after 22 h, *syn*:*anti* = 70:30, ee_{syn}:ee_{anti} = 45%:15%, entry 4).[137] Noteworthy, the enantioselectivity was opposite to the usual one. The diastereoselectivity and the yield of the catalysis rose with the 4-methyl-5-phenyl substituted pyridine bisoxazoline (4*R*,5*R*)-**152** ((4*R*,5*R*)-4-Me-5-PhPyBOx). Nevertheless, the enantioselectivity was lower than with PhPyBOx (71% after 19 h, *syn*:*anti* = 80:20, ee_{syn}:ee_{anti} = 55%:21%, entry 5). Finally, the *tert*-butyl substituted pyridine bisoxazoline furnished a low yield and selectivity but the reaction was *anti*-selective (51% after 21 h, *syn*:*anti* = 35:65, ee_{syn}:ee_{anti} = 8%:44%, entry 6). None of the new ligands tested improved the results obtained with PhPyBOx. Consequently, small tunings of the catalyst composed of (*R*)-PhPyBOx were studied.

The formation of a more soluble complex was first attempted by adding 20 mol% of water, however, the selectivity dropped (67% after 21 h, *syn*:*anti* = 65:35, ee_{syn}:ee_{anti} = 39%:21%, table 28, entry 1). The attempts to use a different non-coordinating counter ion, tetra-3,5-bis(trifluoromethyl)phenylboronate ($TFPB^-$) gave ambiguous results mainly because the final silver salt in the preparation of ^-TFPB was not stable enough to be characterised.[138]

Table 28. Fine tuning of the catalyst using (*R*)-PhPyBOx.[a]



116 **12** *syn*-**145** *anti*-**145**

Entry	Lewis acid	Base	Time (h)	*Syn*:*anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	$Mg(ClO_4)_2(H_2O)_2$	DIPEA	21	65:35	39:21	67
2	$Mg(TFPB)_2$[d]	DIPEA	19	65:35	67:56	63
3	$Mg(MeCN)_6(TFPB)_2$	DIPEA	22	40:60	11:3	5
4	$Mg(Cp)_2$	DIPEA	18	55:45	1:1	49
5	$Mg(ClO_4)_2$	DIPEA	19	85:15	21:63	76[e]
6	$Mg(ClO_4)_2$	DIPEA	16	95:5	4:10	75[f]
7	$Mg(ClO_4)_2$	DIPEA	2	95:5	60:11	72[g]
8	$Mg(ClO_4)_2$	DIPEA	22	75:25	83:82	68[h]
9	$Mg(ClO_4)_2$	DIPEA	20	-	-	0[i]
10	$Mg(ClO_4)_2$	DIPEA	23	80:20	90:85	86[j]
11	$Mg(ClO_4)_2$	TEA	18	80:20	82:83	75[j]
12	$Mg(ClO_4)_2$	$^nBu_3N$	18	85:15	80:76	60[j]
13	-	DIPEA	22	75:25	-	39[j,k]

[a] All reactions: imide (1.0 equiv.), aldehyde (1.1 equiv.), Lewis acid (10 mol%), base (20 mol%) and (*R*)-PhPyBOx (11 mol%). The initial concentration of imide in solution was 1/20 $mol.L^{-1}$. The substrate **116** was added first.

[b] Diastereomeric ratio determined by ^1H NMR.

[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.

[d] Preparation *in situ* from $MgCl_2$ and AgTFPB.

[e] DCM replaced by propionitrile.

[f] DCM replaced by a 1:1 mixture of DCM and THF.

[g] Reaction run at RT.

[h] Filtration of the catalyst.

[i] Long preparation of the catalyst (48 h at RT).

[j] Use of 4 Å MS.

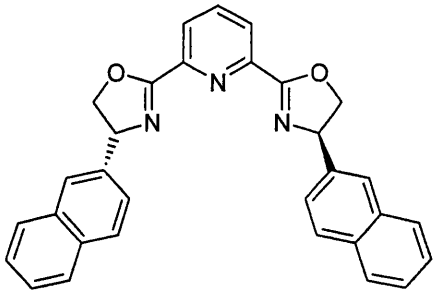
[k] No Lewis acid and no ligand used in this reaction.

When the magnesium salt was formed *in situ*, from $MgCl_2$ and AgTFPB in DCM, the results were promising but the selectivity was not high enough (63% after 19 h, *syn*:*anti* = 65:35, ee_{syn}:ee_{anti} = 67%:56%, entry 2). However, when the magnesium salt was prepared according to the procedure reported for manganese, previous to the reaction, $[Mg(MeCN)_6]TFPB_2$ was formed and the yield and selectivity decreased (5% after 22 h, *syn*:*anti* = 40:60, ee_{syn}:ee_{anti} = 11%:3%, entry 3). Due to the presence of acetonitrile, the magnesium cation may have lost its ability to act as a Lewis acid. The use of magnesium cyclopentadiene, which is soluble in DCM, furnished the *syn*- and *anti*-aldol adducts **145**. A reasonable yield was obtained but no enantioselectivity was detected (49% after 18 h, *syn*:*anti* = 55:45, ee_{syn}:ee_{anti} = 1%:1%, entry 4). This was certainly due to the fact that the two cyclopentadienes were too tightly coordinated to the magnesium cation and impaired the coordination of the ligand. Attempts to solubilise the complex of $Mg(ClO_4)_2$ (10 mol%) and PhPyBOx (11 mol%) and increase the enantioselectivity of the catalysis were then pursued. A reaction in propionitrile furnished the aldol adducts in good yield and the enantioselectivity was reasonably high for the *anti*-aldol adduct but not high enough for the major product, the *syn*-diastereomer (76% after 19 h, *syn*:*anti* = 85:15, ee_{syn}:ee_{anti} = 21%:63%, entry 5). In an attempt to improve the solubilisation of $Mg(ClO_4)_2$ by heteroselective solvation, the solvent was replaced by a one to one mixture of DCM and THF. The yield and diastereoselectivity were excellent (75% after 16 h, *syn*:*anti* = 95:5, entry 6). Nevertheless, the enantioselectivity was low (ee_{syn}:ee_{anti} = 4%:10%). The same diastereoselectivity was achieved in DCM by completing the reaction at room temperature in only 2 hours. The yield was good but the enantioselectivity was not very high (72% after 2 h, *syn*:*anti* = 95:5, ee_{syn}:ee_{anti} = 60%:11%, entry 7). The enantioselectivity of the reaction was the opposite of the reaction at -78 °C, which implies different reaction pathways. In an attempt to remove

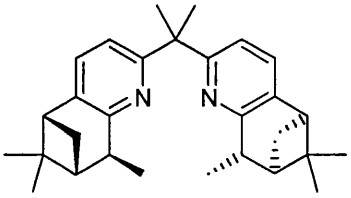
any non-solubilised $Mg(ClO_4)_2$, the catalyst premix was filtered and gave excellent results since the enantioselectivity of both the *syn*- and *anti*-adducts **145** were above 80% (68% after 22 h, *syn*:*anti* = 75:25, ee_{syn}:ee_{anti} = 83%:82%, entry 8). A separate reaction where the catalyst had been premixed for 48 h at room temperature failed to deliver any product after 20 h (entry 9). This was certainly due to the trapping of traces of water despite the care employed to try to render the reaction conditions as anhydrous as possible. An important improvement was observed when using 4 Å MS. The yield of the reaction was high (86% after 23 h at -78 °C, entry 10) and the selectivity exceptional (*syn*:*anti* = 80:20, ee_{syn}:ee_{anti} = 90%:85%). Since the reaction catalysed by the base DIPEA alone at -78 °C furnished the racemic aldol adducts in 39% yield after 22 h (Entry 13), an attempt to improve the selectivity, employing two weaker bases, TEA and $^{n}Bu_3N$ was undertaken. Decreasing the strength of the base lowered the yield (from 86% to 75% and 60% respectively) and the enantioselectivity could not be improved (*ca.* 80%, entries 11 and 12). There is a possibility that NMM which has a much lower pK_a than DIPEA and which also gave reasonable results in the previous base screening, could improve the stereoselectivity of this reaction (Section II 5C, table 19, entry 5). However, this would be at the expense of a lower yield and a longer reaction time.

A few more ligands could perhaps improve the enantioselectivity of this catalytic reaction but time precluded their investigation. Aromatic substituted PyBOx such as the 2-naphthyl substituted pyridine bisoxazoline (*R*)-**155** (Scheme 47), whose synthesis was reported by the group of Desimoni, should provide a more constrained transition state than PhPyBOx.[139] This should also improve the enantioselectivity of the catalyst thanks to the generation of a deeper chiral pocket. Hopefully the bulk of the substituent will not impair the yield of the reaction.

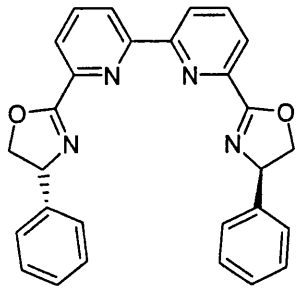
Scheme 47. Various chiral ligands that could improve the selectivity.



(*R*)-155



(-)-156

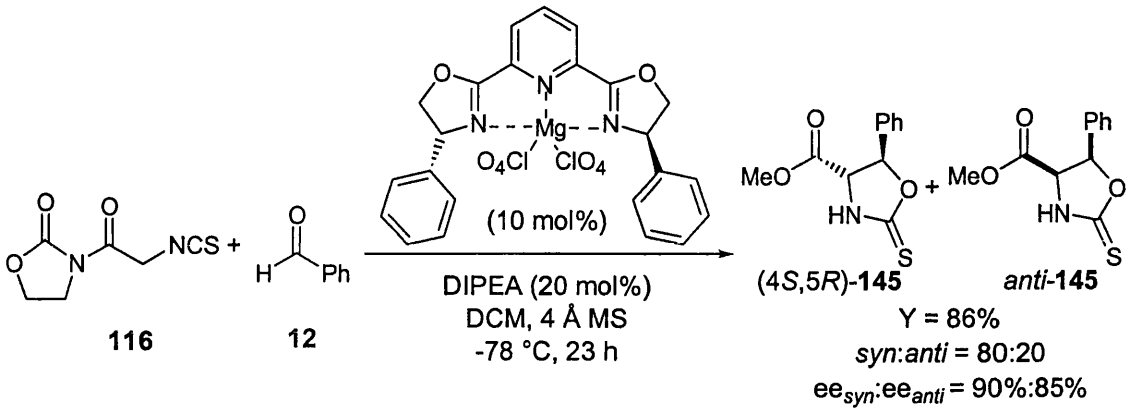


(*R*)-157

Recently Chelucci *et al.* reported a two-step procedure for the synthesis of the chiral C_2-symmetric dipyridylmethane ligand (-)-**156**.[140] They also reported that this ligand furnished good results in a copper catalysed asymmetric cyclopropanation. Therefore, ligand (-)-**156** is potentially an interesting ligand for the asymmetric catalysis under investigation. Moreover, the chiral phenyloxazoline substituted bipyridine (*R*)-**157**, with its four coordination sites, could create an interesting chiral pocket around the Lewis acid which could improve the selectivity of the catalytic aldol reaction.[116]

In conclusion, excellent results have been obtained for the soft enolisation of OxNCSAc **116** and the trapping of the generated metal enolate with benzaldehyde **12** (1.1 equiv.) (Scheme 48). The catalyst was composed of a the Lewis acid, $Mg(ClO_4)_2$ (10 mol%), a chiral ligand (*R*)-PhPyBOx (*R*)-**136** (11 mol%) and DIPEA (20 mol%), a mild base. The reaction was effected at -78 °C in DCM, in the presence of 4 Å MS. The *syn*- and *anti*-aldol adducts **145** were formed in 86% yield after 23 hours with a good *syn*-selectivity (*syn*:*anti* = 80:20) and excellent enantioselectivity (ee_{syn}:ee_{anti} = 90%:85%). As shown below (Section II 6D), the absolute configuration of the major enantiomer for the *syn*-aldol is (4*S*,5*R*).

Scheme 48. Asymmetric aldol reaction.



In addition to the extension of this reaction to more hindered aromatic aldehydes, which could increase the enantioselectivity, the use of a symmetrical starting material could result in a significant degree of chiral amplification. The synthesis of the starting material is presented in the next section.

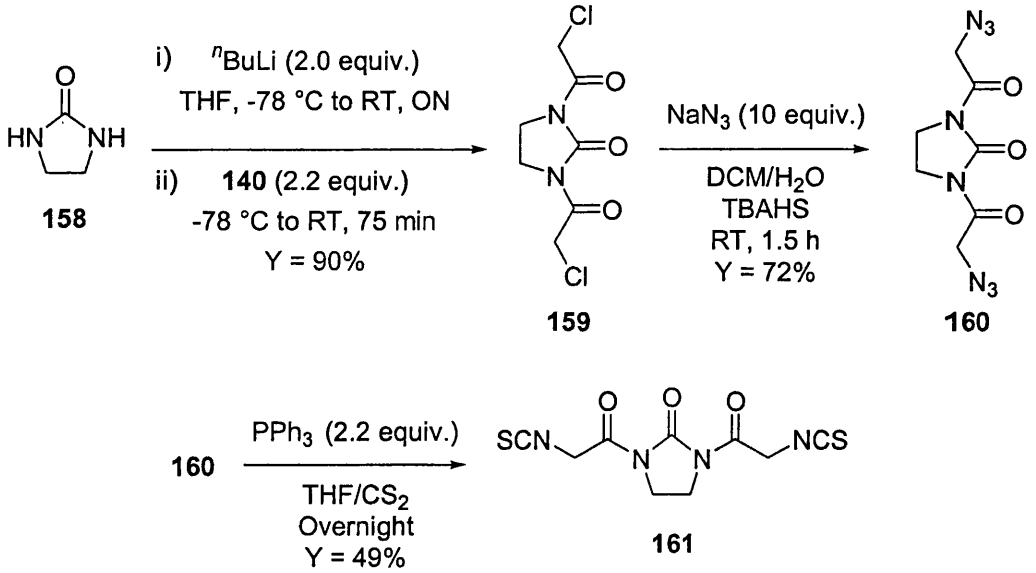
II 6 Ongoing research

This chapter presents the initial results obtained towards the improvement of the enantioselectivity of the catalysis thanks to a technique of chiral amplification derived from Davies's report.[141] This is followed by the initial results of the extension of the catalyst developed in the previous section to a range of aromatic aldehydes. This soft enolisation of isothiocyanate-substituted substrates was briefly applied to several different electrophiles. Finally the absolute configuration of the major adduct is disclosed.

II 6A Chiral amplification

The enantioselectivity of the asymmetric catalytic aldol reaction has reached a ceiling at 90% ee for the *syn*-oxazolidinethiones (4*S*,5*R*)-**145**. An extension from the use of OxNCSAc **116** to the symmetrical *N*,*N*-diisothiocyanatoacetyl-imidazolidinone **161** could offer significant advantages in terms of the ultimate enantioselectivity of the process (Scheme 49). The imidazolidinone **161** was synthesised in a similar manner to the oxazolidinone **116**. The reaction conditions were not optimised. After deprotonation of imidazolidinone **158** by ^{n}BuLi (2.0 equiv.), the temperature was lowered to -78 °C and chloroacetyl chloride **140** (2.2 equiv.) was added. The dichlorodiimide **159** generated was isolated in 90% yield and employed in a nucleophilic substitution to form the symmetrical diazidodiimide **160** (72% yield). Triphenylphosphine (2.2 equiv.) was then added to a solution of diazidodiimide **160** dissolved in THF and carbon disulfide.

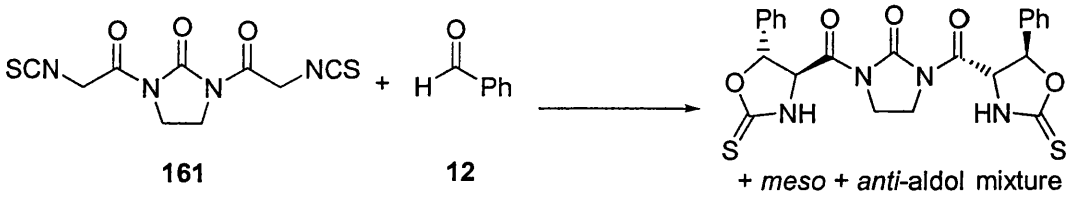
Scheme 49. Symmetrical imidazolidinone **161**.



Due to problems of solubility, the amount of solvent was doubled in comparison to the reaction with the oxazolidinone auxiliary. The final diisothiocyanatoimidazolidinone **161** was isolated in 49% yield.

Davies has shown that similar chiral auxiliaries function effectively in aldol reactions and that the selectivity of each individual addition is independent, no double diastereoselection occurs.[142] If the simple aldol process provides the desired product with an enantiomeric ratio (er = r:s), then in the absence of double diastereoselection, the sum of the products from the symmetrical compound can be described by a simple quadratic equation ($(r + s)^2 = r^2 + 2rs + s^2$), where 2rs is the ratio of *meso*-compounds and ($r^2 + s^2$) is the ratio of C_2-symmetric compounds (desired product) (Scheme 50). Provided that there is a method to separate the C_2-symmetric compound from the meso compound, then the enantiomeric excess of this reaction after purification is ee = $|r^2 - s^2| / (r^2 + s^2)$.[143] For example, with the results obtained previously, er = 95:5 (*i.e.* 90% ee), the C_2-symmetric compound would be obtained in 99% ee.

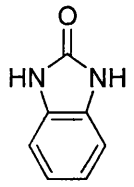
Scheme 50. Major enantiomer expected by chiral amplification.



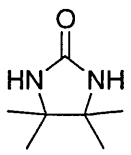
Two reactions using the symmetrical starting material **161** (0.5 equiv.) were attempted. The first one was catalysed by $Mg(ClO_4)_2$ (10 mol%), (*R*)-PhPyBOx (11 mol%) and DIPEA (20 mol%) with benzaldehyde **12** (1.1 equiv.), at -78 °C, in presence of 4 Å MS in the solvent mixture composed of THF and DCM (1:1). This solvent was chosen due to the high diastereoselectivity furnished previously (Table 28, entry 6). The

reaction in DCM at RT that gave access to the same diastereoselectivity but with a higher enantioselectivity was not yet known (Table 28, entry 7). Unfortunately, after prolonged exposure to the catalyst (50 h), only a small amount of new product was detected by TLC. No product could be isolated by column chromatography. Since the solubility of the substituted imidazolidinone **161** was a problem, the second attempt was effected under the same conditions but in the more polar solvent, propionitrile. This solvent had given reasonable results previously, in terms of the yield and diastereoselectivity (Table 22, entry 4), it also dissolved the substrate. However, after 64 h at -78 °C, only traces of a non-symmetrical product were isolated. It is not known why this substrate would not undergo the catalytic aldol reaction but the polarity of this imidazolidinone and the difficulties encountered in dissolving it could be the reasons. Reactions at room temperature might enable the formation of products. Increasing the amount of solvent, in an attempt to dissolve the imidazolidinone in DCM, was not envisaged since the rate of the reaction would have been seriously lowered. Eventually different chelating agents could be employed (Scheme 51). The 2-hydroxybenzimidazole **162** is a commercially available compound and its aromatic ring might improve the solubility of the symmetrical starting material. The synthesis of tetramethyl substituted imidazolidinone **163**, reported by Sayre, could also improve the solubility of the symmetrical starting material.[144]

Scheme 51. Possible auxiliaries for a symmetric starting material.



162



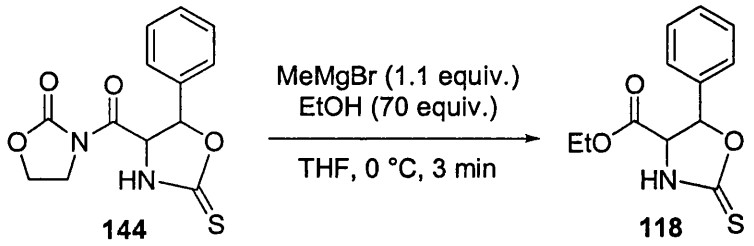
163

The symmetrical starting material **161** prepared for the chiral amplification of the aldol product failed to deliver any product. Some more research on the solvent conditions is still required before ruling out this substrate. Perhaps elevating the temperature could improve the results. Two more auxiliaries **162** and **163** are presented and could possibly lower the polarity of the substrate, which would improve its solubility and enhance the rate of the catalysis. Another attempt to improve the enantioselectivity of the catalytic reaction was to vary the aromatic aldehyde and possibly increase the steric bulk in the transition state. A first attempt is presented in the following section.

II 6B Variation on the aromatic aldehyde

The asymmetric catalytic aldol reaction of OxNCSAc **116** with benzaldehyde **12** (1.1 equiv.) catalysed by $Mg(ClO_4)_2$ (10 mol%), PhPyBOx (11 mol%) and DIPEA (20 mol%) furnished excellent enantioselectivity (ee > 85%). An attempt to generalise this asymmetric catalysis to the addition of OxNCSAc **116** to a range of aromatic aldehydes was briefly investigated. The ethyl esters of a range of aldol adduct had been previously isolated and fully characterised. Therefore, a method to remove the oxazolidinone auxiliary and to form an ethyl ester was envisaged (Scheme 52). No epimerisation at the α-carbon centre was observed with both the *syn*- and *anti*-oxazolidinethiones **144**. When the *syn*-oxazolidinethione *syn*-**144** (de = 99%) was subject to ethanolysis conditions, *i.e.* MeMgBr (1.1 equiv.) in EtOH and THF at 0 °C for 3 min, the *syn*-ester **118** was formed in 78% yield (de = 99%). Similarly, when the *anti*-oxazolidinethione **144** (de = 99%) was ethanolysed, the ester *anti*-**118** was obtained in 91% yield (de = 99%).

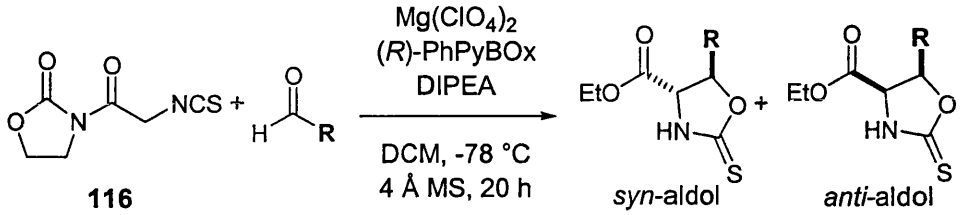
Scheme 52. Ethanolysis of the imide **144**.



A range of aromatic aldehydes was then used to trap the chiral enolate formed by the catalytic reaction of OxNCSAc **116** and $Mg(ClO_4)_2$ (10 mol%), (*R*)-PhPyBOx (*R*)-**136** (11 mol%) and DIPEA (20 mol%) in DCM, at -78 °C and in the presence of 4 Å MS following the typical procedure in section III 5. The initial results were low but time precluded the repetition of the reactions (Table 29). Except for the reactions with 2-bromo and 3-bromobenzaldehyde (Entries 4 and 5), every yield was above 58%. For the catalysis with benzaldehyde, *para*-bromobenzaldehyde, *para*-anisaldehyde and 2-naphthaldehyde, the diastereoselectivity of the reaction was improved in comparison to the reaction with the ester **117** (*syn*:*anti* > 70:30, entries 1, 6-8). More disappointingly, the enantioselectivity observed in these reactions were all bellow 80% ee. Knowing the susceptibility of the catalyst to traces of water or any small amount of impurity that could bind to the cation, the quality of the Lewis acid or of the substrate OxNCSAc **116** was blamed and seems reasonable as a test reaction on benzaldehyde gave only 66% ee (Table 29, entry 1). The *para*-nitro aldol adducts **121** could not be separated by chiral HPLC (Entry 2). The *para*-cyano aldol adducts **122** gave the lowest enantioselectivity (ee_{syn} = 11%, entry 3). The standard reaction with trapping by benzaldehyde **12** and methanolysis work-up was repeated twice on a gram scale, changing the batches of Lewis acid and starting material. The aldol adducts were formed in good yield (Y > 77% after 22 h at -78 °C). The enantioselectivity was just under the previous excellent results reported (ee_{syn}:ee_{anti} > 86%:79%). Consequently, this screening of aromatic

aldehydes will require extra care in the preparation step, to provide conditions as anhydrous as possible and to prevent any deactivation of the asymmetric catalyst.

Table 29. Screening of aromatic aldehydes.[a]



Entry	R	Products	*Syn:anti*[b]	ee_{syn}:ee_{anti} (%:%)[c]	Yield (%)
1	C_6H_5	**118**	75:25	66:39	66
2	4-NO_2-C_6H_4	**121**	55:45	-	66
3	4-CN-C_6H_4	**122**	65:35	11:38	58
4	2-Br-C_6H_4	**123**	50:50	36:57	39
5	3-Br-C_6H_4	**124**	45:55	38:55	40
6	4-Br-C_6H_4	**125**	70:30	45:73	72
7	4-OMe-C_6H_4	**127**	85:15	77:68	59
8	2-naphthyl	**128**	75:25	77:68	59

[a] All reactions: imide(1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), DIPEA (20 mol%) and (*R*)-PhPyBOx (11 mol%). The initial concentration of imide in solution was 1/20 mol.L^{-1}. The substrate **116** was added first.

[b] Diastereomeric ratio determined by ^1H NMR.

[c] Enantiomeric excess determined by Chiral HPLC using a Chiracel OD column.

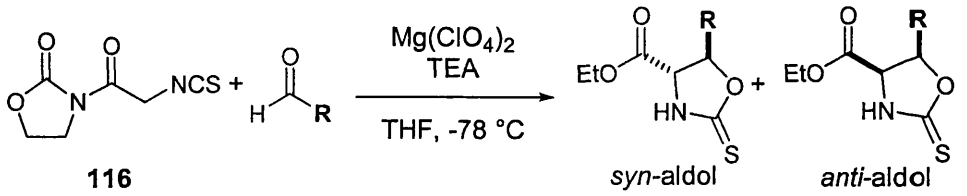
II 6C Trapping by various electrophiles

The catalytic aldol reaction of OxNCSAc was undertaken with four different aldehydes in order to expend the scope of the reaction. Initial results are presented in this section. In addition, an attempt to extend this soft enolisation process to the Michael

addition was envisaged. This attempt gave low yields but promising results. Finally, a catalytic imine-aldol reaction was developed and is presented.

Since the catalytic aldol reaction gave good results with aromatic aldehydes, it was interesting to extend this reaction to other types of aldehydes. The initial results of the reaction of OxNCSAc with four different aldehydes, following the general procedure proposed in section III 7, were promising. The catalyst was composed of $Mg(ClO_4)_2$ (10 mol%) and TEA (20 mol%). No ligand was employed as this catalyst proved more efficient in the generation of the aldol product (Section II 5D, table 21, entry 2). After 2 hours at -78 °C, the reaction of OxNCSAc **116** with *trans*-cinnamaldehyde delivered the oxazolidinethione **165** in 26% yield and good *syn*-selectivity (*syn*:*anti* = 70:30, table 30, entry 1). The reaction rate was slower than for benzaldehyde and increasing the temperature or reaction time would certainly increase the yield of the reaction as starting material was recovered.

Table 30. Extension of the scope of the aldol reaction to various aldehydes



116 *syn*-aldol *anti*-aldol

Entry	R	Time (h)	Products	*Syn*:*anti*[b]	Yield (%)
1	(*E*)-Styryl	2	**165**	70:30	26
2	^{n}Propyl	2	**166**	50:50	41
3	^{c}Hexyl	3	**167**	50:50	41
4	^{t}Butyl	3	**168**	100:0	4

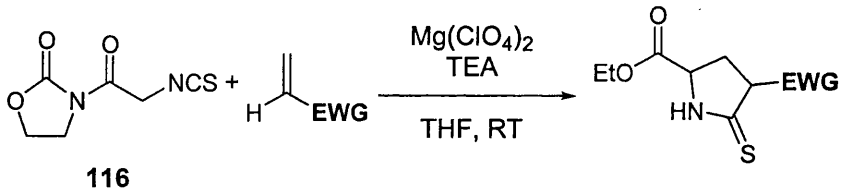
[a] All reactions: imide(1.0 equiv.), aldehyde (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%), and TEA (20 mol%).

[b] Diastereomeric ratio determined by ^{1}H NMR.

The non-aromatic aldehydes, butyraldehyde and cyclohexylcarboxaldehyde, both formed the aldol adducts **166** and **167** respectively in 41% (Entries 2 and 3). For these two reactions, no diastereoselection was observed. However, the reaction with pivaldehyde only formed one diastereomer, the *syn*-aldol **168**, but the yield of the reaction was very low (4% after 3 h at -78 °C, entry 4). This was certainly due to the steric bulk of the *tert*-butyl substituent. The starting materials were recovered and increasing the reaction time or temperature should enhance the yields of these three reactions.

The Michael addition of OxNCSAc **116** to three conjugated alkenes was also briefly investigated. The substituted thiolactam generated is an interesting synthon that was used, by Hasegawa and co-workers, as an intermediate for the synthesis of hepatoprotective agents.[145] The reaction with the ethyl acrylate formed no product, even after 22 hours at room temperature (Table 31, entry 1).

Table 31. Attempts to deliver substituted thioxopyrrolidines.



116

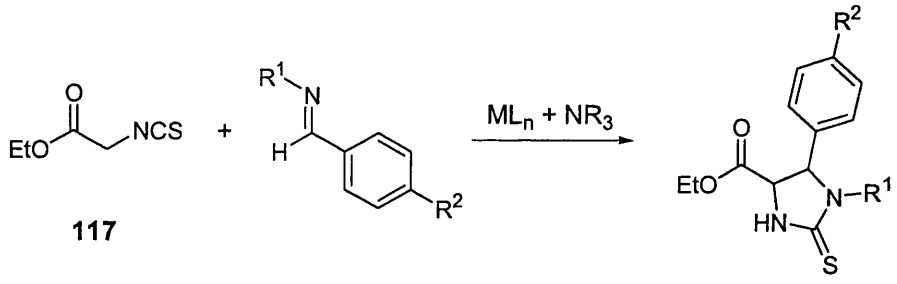
Entry	EWG	Time (h)	Products	Yield (%)
1	CO_2Et	22	-	0
2	SO_2Ph	4	**169**	2
3	CN	4	**170**	5

[a] All reactions: imide(1.0 equiv.), alkene (1.1 equiv.), $Mg(ClO_4)_2$ (10 mol%) and TEA (20 mol%).

Traces of product (2% and 5%) could be isolated while using the more reactive phenylvinylsulfone and the acrylonitrile respectively (Entries 2 and 3). Overall, the catalyst failed to deliver significant quantities of product and more work towards this aspect of the catalysis is still required.

Finally, this project was extended to a catalytic imine-aldol reaction of ethyl isothiocyanatoacetate **117** and several tosylimines (Scheme 53). Imine-aldol reaction and post addition cyclisation of the isothiocyanate substituent with the newly generated amine have been reported by Volkmann *et al.*[146] The formation of an imidazolidinethione should prevent the epimerisation at the α-carbon centre. This protected α,β-diaminoacid has important potential applications, including the formation of β-lactams, scaffolds for some of the most important antibiotics.[147]

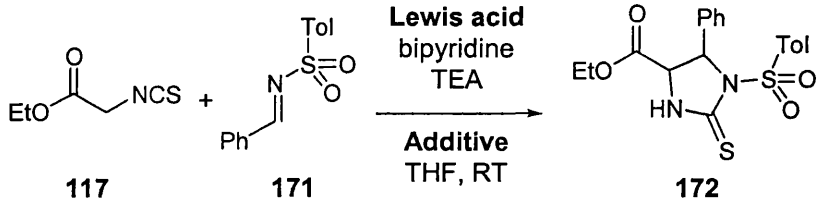
Scheme 53. Imine-aldol reaction using ethyl isothiocyanatoacetate **117**.



The initial reaction used the catalyst developed for the racemic aldol reaction, *i.e.* $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%) and TEA (20 mol%) in THF at RT. A first attempt to react the ester **117** (1.0 equiv.) with *N*-4-methoxybenzilidenaniline (1.1 equiv.) failed to form any product. A competitive reaction including the 4-methoxybenzaldehyde in addition of the imine, formed the aldol adduct **127** in 40% yield (max expected 50%). This demonstrated that the imine was only lacking reactivity but was not quenching the catalyst since aldol reaction was observed. Therefore, the

more reactive *N*-tosylimine **171** that has already been reported to undergo imine-aldol reaction, was subsequently used (Table 32).[148,149] After 19 hours at room temperature, only 2% of the imidazolidinethione **172** could be isolated (Entry 1). The group of Frost reported the activation of imines in hetero Diels-Alder reactions using as little as 0.5% of indium triflate.[150] Consequently, the next reaction included 1% of $In(OTf)_3$ (Entry 2). After 24h, the product **172** was isolated in 16% yield. The perchlorate counter ions on the magnesium were next replaced by triflates (Entry 3). The product was then obtained in 28% yield after 22 hours at RT. The anion perchlorate was deemed incompatible with the imine-aldol catalysis and was thought to lower the activity of the indium due to ion exchange.

Table 32. Determination of the conditions for the imine-aldol catalysis.[a]



117 **171** **172**

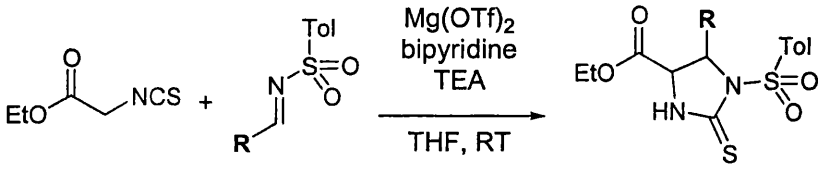
Entry	Lewis acid	Additive	Time (h)	Yield (%)
1	$Mg(ClO_4)_2$	-	19	2
2	$Mg(ClO_4)_2$	$In(OTf)_3$	24	16
3	$Mg(OTf)_2$	$In(OTf)_3$	22	28
4	$Mg(OTf)_2$	-	24	54
5	$Mg(OTf)_2$	-	26	48[b]

[a] All reactions: ester (1.0 equiv.), imine (1.1 equiv.), Lewis acid (10 mol%), TEA (20 mol%) and bipyridine (10 mol%); Additive (1 mol%).
[b] Imine (3.0 equiv.).

However, the indium was not necessary for this reaction and actually permitted the generation of $Mg(OTf)_2$ from $Mg(ClO_4)_2$. Indeed, the reaction catalysed by $Mg(OTf)_2$

(10 mol%), and TEA (20 mol%), without additive, formed the adduct in 54% yield after 24 hours (Entry 4). In an attempt to increase the yield and the rate of reaction, three equivalents of imine were used. However, after 26 h at RT, the product was only formed in 48% yield (Entry 5). The catalyst developed for the imine-aldol reaction of ethyl isothiocyanatoacetate **117** with the imine **171** was next employed to determine the scope of this catalysis with a range of substituted tosylimines. Following the general procedure, section III 8, $Mg(OTf)_2$ (10 mol%), bipyridine (10 mol%) and TEA (20 mol%) were employed to catalyse the imine-aldol reaction of ethyl isothiocyanatoacetate **117** (1.0 equiv.) with four different *N*-tosyl-arylimines (2.0 equiv.) (Table 33). The use of two equivalents of the non-substituted imine improved the yield of formation of **172** to 67% after 18 h (Entry 1). The reaction with the *para*-cyano substituted arylimine furnished the adduct **173** in good yield (77% after 18 h, entry 2). The *para*-methoxy substituted arylimine furnished the adduct **174** in lower yield (44% after 28 h, entry 3). However, in comparison with the previous imidazolidinethiones, the diastereoselectivity of the reaction was improved (*syn*:*anti* = 75:25). The 2-naphthyl substituted imine furnished the adduct **175** in good yield but with the lowest diastereoselectivity (75 % yield after 17 h, *syn*:*anti* = 55:45, entry 4). One problem encountered during this screening of imine was the decomposition of the unreacted imine on the silica column, which contaminated some of the products and could not be resolved by recrystallization of the imidazolidinethione *anti*-**175**. Interestingly, the lack of ligand decreased the yield of the reaction, which indicates the possibility of asymmetric induction while using a chiral ligand.

Table 33. Variation on tosylimine.[a]



117

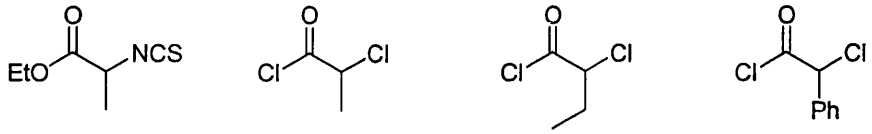
Entry	R	Product	Time (h)	(*syn*:*anti*)	Yield (%)
1	C_6H_5	**172**	18	65:35	67
2	C_6H_4CN	**173**	18	60:40	77
3	$C_6H_4OCH_3$	**174**	28	75:25	44
4	2-Naphthyl	**175**	17	55:45	75

[a] All reactions: ester (1.0 equiv.), imine (2.0 equiv.), $Mg(OTf)_2$ (10 mol%), TEA (20 mol%) and bipyridine (10 mol%).

In conclusion, these initial attempts to expand the scope of the catalyst developed for the aldol reaction of isothiocyanate-substituted substrates with aromatic aldehydes furnished promising results. In the case of aldehydes, the optimisation of the temperature, and reaction time should improve the yield; using a chiral ligand should give access to an asymmetric catalyst. For the Michael addition, unfortunately, the products were formed in very low yield and the development of an appropriate catalyst is still required. Concerning the imine-aldol catalysis, changing the perchlorate counter ion for a triflate counter ion formed a good catalyst that should efficiently transfer the asymmetry of a chiral ligand to the product. The use of different nucleophiles; either commercially available (ethyl 2-isothiocyanatopropionate **176**) or prepared in a few steps, like OxNCSAc **116**, from commercially available 2-chloro-substituted acyl chlorides (2-chloropropionyl chloride **177**, 2-chlorobutiryl chloride **178** and 2-chloro-2-phenylacetyl chloride **179**) should be well tolerated by the catalyst developed for ethyl

isothiocyanatoacetate and OxNCSAc (Scheme 54). This would increase the scope of the catalyst and give access to more substituted oxazolidinethiones.

Scheme 54. Ester and 2-chloro-substituted acyl chlorides commercially available.



176 **177** **178** **179**

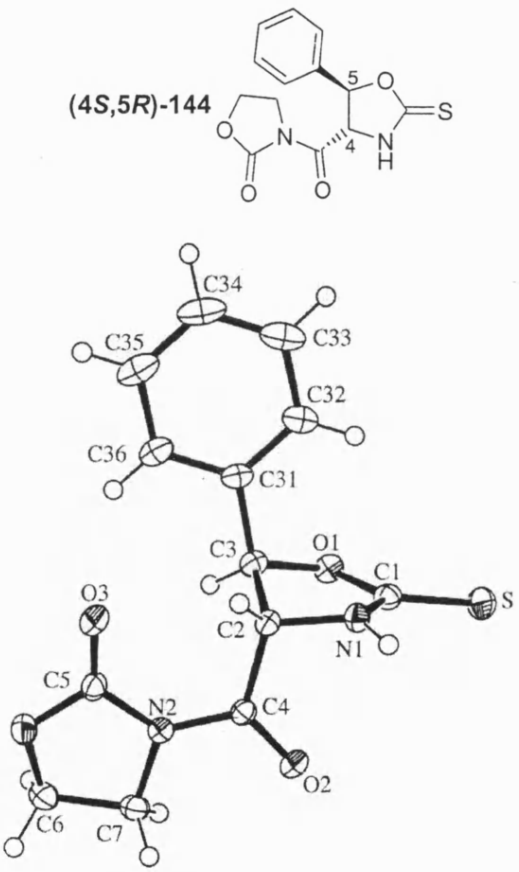
The use of other substituents for the cyclisation like isocyano-, isocyanato- and triphenylphosphazo-substituted nucleophiles is still to be investigated.

II 6D Absolute configuration and transition state

To complete the study and understand the mechanism of this catalytic aldol reaction, the determination of the absolute configuration of the adducts was necessary. A crystal structure of the Lewis acid $Mg(ClO_4)_2$ complexed by the chiral ligand (*R*)-PhPyBOx (*R*)-**136** and the chelating substrate OxNCSAc **116**, would also be of precious benefit. However, time precluded the obtention of this second parameter. Attempts to determine the absolute configuration of the major enantiomer, by formation of the unprotected *β*-hydroxy-*α*-amino acid from the oxazolidinethione **144**, and comparison to the literature data of 3-hydroxyphenylalanine, failed to deliver the pure amino acid after recrystallization.[151,152] A purification of the amino acid on DOWEX resin, like proposed by Seebach *et al.* may deliver the expected molecule.[153] Another interesting alternative for the determination of the absolute configuration was the formation of the enantiomerically pure oxazolidinethione *syn*-**144** using the catalytic asymmetric synthesis, crystallisation of the product and X-ray diffraction experiment (Scheme 55).

The *syn*-**144** aldol adduct was purified by column chromatography and two consecutive recrystallizations from DCM-hexane. Long flat crystals were gathered and used for the X-ray experiment.

Scheme 55. Oxazolidinethione product (4*S*,5*R*)-**144** and X-Ray crystal structure.

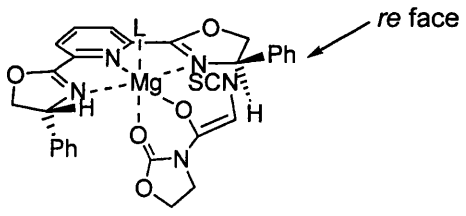


As expected from the small value of the coupling constant between 4-H and 5-H (J = 2.7 Hz), the X-ray experiment demonstrated that this sample was a *syn*-aldol adduct. The absolute configuration was (4*S*,5*R*). The enantiomeric excess was determined by HPLC after methanolysis ($ee_{(4S,5R)}$ = 99.9%). The comparison of this methyl ester sample ($[\alpha]_D^{21}$ = +27.8° (c = 0.53, DCM)), to the previously reported ester *syn*-**145** (ee_{syn} = 90%, $[\alpha]_D^{21}$ = +30.2° (c = 3.4, DCM)) permitted to conclude that the major

enantiomer was the ester (4*S*,5*R*)-**145** generated from the imide (4*S*,5*R*)-**144**. The first value of specific rotation, +27.8°, was smaller than expected, but this was certainly due to the small amount of product available and the presence of residual solvent in the sample.

A hypothetical intermediate is then proposed and is in agreement with the absolute configuration of the major aldol adduct (4*S*,5*R*). The tetrahedral transition state reported for different magnesium(II) catalysts in the literature could not suit the geometry of the PyBOx ligand and was ruled out.[122,154,155] However, the octahedral magnesium(II) is presented below (Scheme 56). The chelating OxNCSAc **116** first coordinates to the magnesium cation and is subsequently enolised by the mild base DIPEA to form preferentially a (*Z*)-enolate. ^{13}C NMR experiments would certainly help to determine the ratio of (*E*) and (*Z*)-enolates. The chelation of the substrate **116** accounts for the improvement of enantioselectivity *versus* the ester substrate **117**. The *re* face of the enolate is hindered by the phenyl substituent on the chiral ligand (*R*)-**136**. The attack from the *si* face of the (*Z*)-enolate furnishes the 4*S* absolute configuration. If the reaction proceeds through a cyclic transition state then the benzaldehyde **12** should coordinate to the remaining axial position. However, the distance between the two reacting carbons seems too long for this cyclic transition step to happen. The aldehyde could either be activated by a second molecule of catalyst or react without activation by a Lewis acid. Finally, the formation of crystals of $Mg(ClO_4)_2$ coordinated with the chiral ligand and the starting materials, as well as ^{13}C NMR experiments will surely bring light to this step of the catalysis and are currently under investigation.

Scheme 56. Postulated (*Z*)-enolate intermediate.



L = ClO_4^- or aldehyde

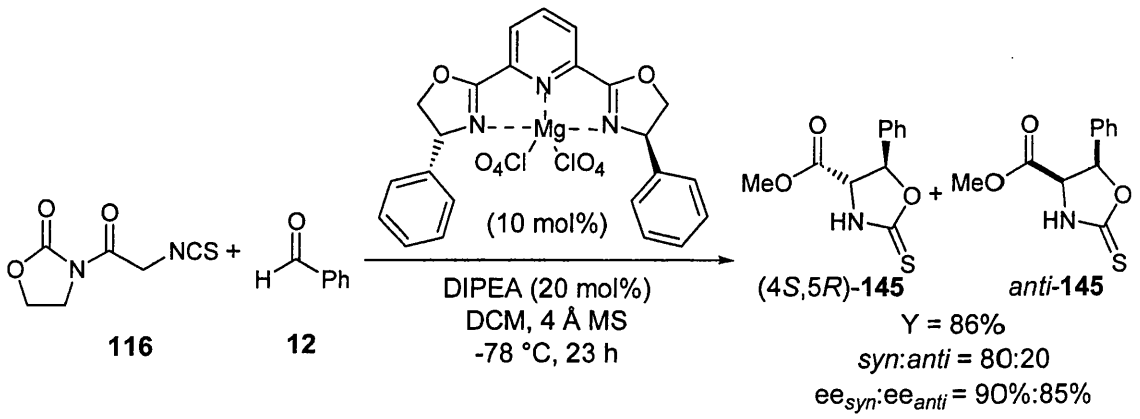
II 7 Conclusion

β-Hydroxy-*α*-amino acids are important molecules in organic chemistry. They can be accessed through the aldol reaction. An attractive method to obtain these molecules is to generate the enolate *in situ* by a technique of soft enolisation, *i.e.* the combination of a Lewis acid and a tertiary amine. Following the recent report of catalytic soft enolisation of 1,3-dicarbonyl compounds by Ji and Barnes, promoted by $Mg(OTf)_2$ and NMM, we envisaged the catalytic generation of *α*-substituted chiral enolates and their trapping by aldehydes.[102] Post aldol reaction, an isothiocyanate substituent on the nucleophile enables the cyclisation with the newly generated hydroxide. The formation of oxazolidinethiones prevents the epimerisation of the *α*-carbon centre as well as the sequestration of the catalyst by the hydroxy functionality. The first part of the project focused on the determination of a suitable combination of Lewis acid and base that promotes the reaction, using commercially available ethyl isothiocyanatoacetate **117** and benzaldehyde **12** (1.1 equiv.). After intensive screening of bases, metal salts, solvents and additives, excellent catalytic conditions were discovered: $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%) and TEA (20 mol%) in THF at 0 °C. The *syn*- and *anti*-oxazolidinethiones **118** were formed in excellent yield and moderate *syn*-selectivity (Y = 86% after 21 h, *syn*:*anti* = 65:35).

This method was general to a range of aromatic aldehydes and furnished good results. However, when we tried to extend this catalyst to an asymmetric version by employing chiral ligands, low degrees of enantioselectivity were observed. The benzyl substituted chiral bisoxazoline (*R*)-**132** gave both a poor yield and poor enantioselectivity (Y = 8%, ee_{syn} = 18%).

A two-point binding nucleophile **116** was prepared and used to develop the asymmetric method. A meticulous screening of bases, solvents, chiral ligands and temperatures created excellent conditions for the asymmetric catalytic aldol reaction. The phenyl substituted chiral pyridine bisoxazoline (*R*)-**136** (11 mol%), combined with $Mg(ClO_4)_2$ (10 mol%) and DIPEA (20 mol%) formed an efficient catalyst for the aldol reaction of imide **116** with benzaldehyde **12** (1.1 equiv.) (Scheme 57). The methyl esters *syn*- and *anti*-**145** were generated in 86% yield after 23 h at -78 °C in DCM in the presence of 4 Å MS. The selectivity of the reaction was excellent (*syn*:*anti* = 80:20, ee_{syn}:ee_{anti} = 90%:85%).

Scheme 57. Asymmetric aldol reaction.



The conditions of this new catalyst were finally used with various aromatic aldehydes, but time precluded the enhancement of these reactions. Promising results

were also obtained with different types of aldehydes. An optimisation of conditions for the racemic aldol reaction should be transferable to the asymmetric catalytic aldol reaction. The aldol reaction with a second α-substituent on the nucleophile is also envisaged and should be straightforward. The trapping of the enolate with Michael electrophiles gave very low yields and an efficient catalyst still needs to be developed for this transformation. Concerning the imine-aldol reaction, good results have been obtained by changing $Mg(ClO_4)_2$ for $Mg(OTf)_2$. The method was applied to a range of *N*-tosyl arylimines and the use of a chiral ligand should form enantiomerically enriched imidazolidinethiones **172-175**, *i.e.* protected α,β-diaminoacids.

The absolute configuration of the *syn*-aldol adduct (4*S*,5*R*)-**144** was determined by X-ray experiment. Time precluded the formation of crystals of $Mg(ClO_4)_2$, complexed by the chiral ligand (*R*)-**136**, the imide **116** and benzaldehyde **12**, but this is under investigation and should provide interesting insight into the transition state of this catalytic transformation.

III Experimental

III 1 General information

All reactions were performed under an inert atmosphere of nitrogen, in oven or flame dried glassware unless otherwise stated. Nitrogen was passed through a Drierite® filled drying tube before use.

The solvents used in the reactions were distilled prior to use from the relevant drying agent. Toluene, hexane, ether and THF were distilled from sodium metal. DCM, chloroform, acetonitrile and propionitrile were distilled from calcium hydride. Petrol refers to petroleum spirit 40-60 °C.

Analytical thin layer chromatography was carried out using precoated aluminium-backed silica plates (Merck Kieselgel $60F_{254}$). Plates were visualised under ultraviolet light or by staining with $KMnO_4$. Flash chromatography was carried out using Merck Kieselgel 60H silica and Fisher Matrex Silica 60 silica. Pressure was applied at the column head with hand bellows. Columns were collected and monitored by TLC.

Melting points were determined using a Büchi 535 melting point apparatus and are reported uncorrected. Infrared measurements were carried out as solutions in a 0.5 mm NaCl cell or as a KBr disc using a Perkin-Elmer 1600 series FTIR spectrometer with internal calibration in the range 4000-500 cm^{-1}. Mass spectra were carried out on a Finnigan MAT 8340 instrument at the University of Bath or on a Micromass Quatro II and Finnigan MAT 95XP by the EPSRC mass spectrometry service at the University of Wales, Swansea. Elemental analysis was performed on an Exeter Analytical CE440 Elemental Analyser at the University of Bath.

^{1}H, ^{13}C and ^{31}P nuclear magnetic resonance experiments were recorded using a Brüker AC-300 MHz NMR spectrometer or on a Jeol 400 MHz NMR spectrometer. Chemical shifts were reported in part per million from tetramethylsilane for ^{1}H and ^{13}C experiments and from 85% H_3PO_4 as an external reference for ^{31}P experiments. The residual solvent pick was used as an internal standard. The multiplicities of the spectra are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Sometimes, we observed apparent multiplicities (app.). Coupling constants (*J*) are given in Hz. Phosphorous experiments were proton decoupled.

Optical rotations were performed on an Optical Activity LTD: AA-10 automatic polarimeter.

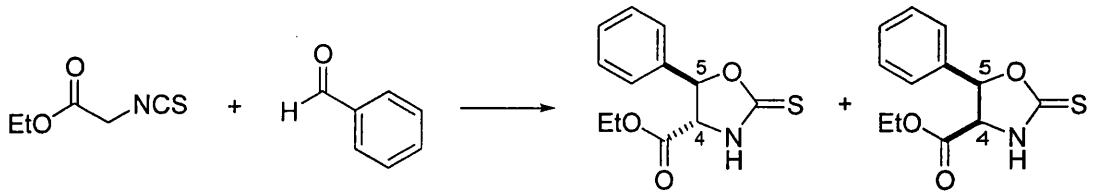
Analytical high performance liquid chromatography was carried out using Thermo Separation Products (TSP) spectra SERIES P200, using the Chiralcel® OD00CE-IJ033 column. The loading loop was 20 µL. The eluant employed was an isocratic mixture of hexane and IPA (80:20 respectively) at a flow of 1 $mL.min^{-1}$. A TSP spectra SERIES UV100 detector was fitted to the outlet of the column and indicated the absorption at 254 nm, r = 0.0005. Retention times are reported in minutes. The enantiomeric excess were calculated form the integration of the absorption picks at 254 nm.

All chemicals were purchased from Acros, Aldrich, Avocado, Lancaster or Strem chemical companies and were used after distillation for the liquids but without further purification for the solids.

2,6-Bis-[(4'*S*)-4'-benzyloxazolin-2'-yl]-pyridine,[156] 2,6-bis-[(4'*S*)-4'-*tert*-butyloxazolin-2'-yl]-pyridine,[36] (1*R*,2*R*)-*N*,*N*'-bis-(2',6'-dichlorobenzylidene)-diaminocyclohexane,[126] 2,2-bis-[(4'*R*,5'*S*)-4',5'-diphenyloxazolin-2'-yl]-propane,[157] 2,6-bis-[(4'*R*,5'*R*)-4',5'-diphenyloxazolin-2'-yl]-pyridine, 1,2-bis-[(4'*R*)-4'-phenyloxazolin-2'-yl]-benzene,[124] 2,2-bis-[(4'*S*)-4'-*iso*-propyloxazolin-2'-yl]-

propane,[158] {3a*S*-[2(3'a*R**,8'a*S**),3aα,8aα]}-2,2'-(cyclopropylidene)-bis-{3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole},[102] (*R*,*R*)-4,6-dibenzofurandiyl-2,20-bis-(4-phenyloxazoline),[159] {3a*S*-[2(3'a*R**,8'a*S**),3aα,8aα]}-2,2'-(1-methylethylidene)-bis-{3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole},[160] {3a*S*-[2(3'a*R**,8'a*S**),3aα,8aα]}-2,2'-(2,6-pyridinediyl)-bis-{3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole},[134] silver tetra-3,5-bis(trifluoromethyl)phenylboronate,[138] *N*-(4-toluenesulphonyl)benzaldimine,[161] *N*-(4-toluenesulphonyl)-4-cyanobenzaldimine,[162] *N*-(4-toluenesulphonyl)-2-naphthaldimine,[163] *N*-(4-toluenesulphonyl)-4-methoxybenzaldimine,[164] were prepared as described in the literature.

III 2 Preparation of (4*S**,5*R**)-5-phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-118 and (4*R**,5*R**)-5-phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-118; serving as a typical experimental procedure for the screening of catalysts and aldehydes with ethyl isothiocyanatoacetate 117



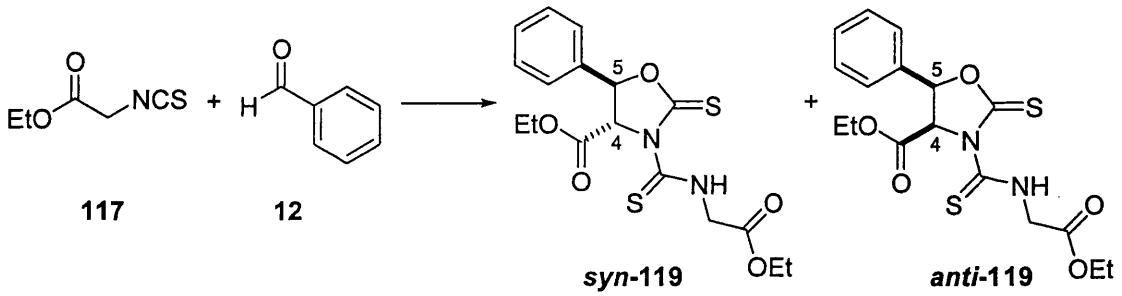
117 **12** ***syn*-118** ***anti*-118**

A mixture of $Mg(ClO_4)_2$ (31 mg, 0.14 mmol) and bipyridine (22 mg, 0.14 mmol) in dry THF (5.5 mL) was stirred for 10 min under nitrogen at RT prior to the addition of triethylamine (39 μL, 0.28 mmol). The mixture was cooled to 0 °C. After 10 min ethyl isothiocyanatoacetate **117** (170 μL, 1.38 mmol) and benzaldehyde **12** (150 μL, 1.52

mmol) were added. After a further 21 h of stirring at 0 °C, the reaction was quenched with saturated (sat.) aqueous ammonium chloride solution (5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The organic portions were combined and washed with sat. aqueous copper sulphate solution (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM-EtOAc, 98:2) to give in order of elution the *syn*-oxazolidinethione[104] ***syn*-118** (208 mg, 60%), as white crystals: mp 107 °C (EtOAc-petrol); R_f(SiO_2, $CHCl_3$-EtOAc, 75:25) 0.53; ν_{max}($CHCl_3$, 0.05 M)/cm^{-1} 3426 (NH), 2952 (CH), 1748 (C=O), 1486 (NHC=S), 1177 (CO); δ_H(400 MHz; $CDCl_3$) 7.94 (1H, s, NH), 7.46-7.38 (5H, m, C_6H_5), 5.98 (1H, d, *J* 6.1, 5-H), 4.49 (1H, d, *J* 6.1, 4-H), 4.40-4.26 (2H, m, CH_2), 1.40 (3H, t, *J* 7.0, CH_3); δ_C(100 MHz; $CDCl_3$) 189.9, 168.2, 137.0, 129.7, 129.3, 125.9, 85.9, 64.9, 63.4, 14.5; *m/z* (EI) 251 (M^+, 25%), 91 (C_7H_7, 100), 77 (C_6H_5, 78), 45 (C_2H_5O, 11); (Found: MH^+, 252.0695. $C_{12}H_{14}NO_3S$ requires *M*, 252.0694); and the *anti*-oxazolidinethione ***anti*-118** (89 mg, 26%), as white crystals: mp 114 °C (EtOAc-petrol); R_f(SiO_2, $CHCl_3$-EtOAc, 75:25) 0.38; ν_{max}($CHCl_3$, 0.05 M)/cm^{-1} 3426 (NH), 2964 (CH), 1749 (C=O), 1486 (NHC=S), 1176 (CO); δ_H(400 MHz; $CDCl_3$) 7.59 (1H, s, NH), 7.42-7.20 (5H, m, C_6H_5), 6.09 (1H, d, *J* 9.8, 5-H), 4.91 (1H, d, *J* 9.8, 4-H), 3.80 (1H, dq, *J* 10.7, 7.2, CH_AH_B), 3.67 (1H, dq, *J* 10.7, 7.2, CH_AH_B), 0.82 (3H, t, *J* 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 190.0, 167.3, 133.4, 129.9, 128.8, 126.9, 85.5, 63.0, 62.5, 13.9; *m/z* (EI) 251 (M^+, 16%), 91 (C_7H_7, 100), 77 (C_6H_5, 63); (Found: MH^+, 252.0696. $C_{12}H_{14}NO_3S$ requires *M*, 252.0694).

The enantiomers of ***syn*-118** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 7.5 min and tr_2 = 9.0 min; the enantiomers of ***anti*-118** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 11.8 min and tr_2 = 32.3 min.

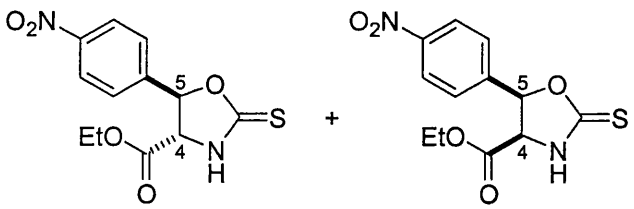
Preparation of (4*S,5*R**)-3-ethoxycarbonylmethylthiocarbamoyl-5-phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-119 and (4*R**,5*R**)-3-ethoxycarbonylmethylthiocarbamoyl-5-phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-119**



To a solution of $Mg(OTf)_2$ (0.44 g, 1.38 mmol) and triethylamine (1.92 mL, 13.8 mmol) in THF (55 mL) were added ethyl isothiocyanatoacetate **117** (1.71 mL, 13.8 mmol) and benzaldehyde **12** (1.54 mL, 15.2 mmol). After 4 days of stirring at RT, the reaction was quenched with saturated aqueous ammonium chloride solution (50 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 100 mL). The organic portions were combined, washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, petrol-EtOAc, 90:10) to give in order of elution the *syn-oxazolidinethione syn*-**119** (562 mg, 20%) as a colourless oil: R_f(SiO_2, petrol-EtOAc, 80:20) 0.26; ν_{max}($CHCl_3$, 0.025 M)/cm^{-1} 3118 (NH), 2941 (CH), 1748 (C=O), 1538 (NHC=S); δ_H(300 MHz; $CDCl_3$) 12.24 (1H, s, NH), 7.47-7.34 (5H, m, C_6H_5), 5.78 (1H, d, *J* 3.8, 5-H), 5.60 (1H, d, *J* 3.8, 4-H), 4.42 (1H, d, *J* 2.3, 3-NH-CH_AH$_B$), 4.41 (1H, d, *J* 2.3, 3-NH-CH$_A$$H_B$), 4.39 (2H, m, 4-C$H_2CH_3$), 4.28 (2H, q, *J* 7.1, 3-OCH_2CH$_3$), 1.34 (3H, t, *J* 7.1, 4-CH$_2$CH_3), 1.32 (3H, t, *J* 7.1, 3-CH$_2$CH_3); δ_C(75 MHz; $CDCl_3$) 182.4, 177.5, 167.9,

167.7, 136.0, 129.9, 129.4, 125.3, 81.2, 70.6, 62.8, 62.0, 48.5, 14.2, 14.1; *m/z* (ES) 396 (M^+, 100%); (Found: MH^+, 397.0884. $C_{17}H_{21}N_2O_5S_2$ requires *M*, 397.0886); and the *anti-oxazolidinethione anti*-**119** (375 mg, 14%) as white crystals: mp 138 °C (EtOAc-hexane); R_f(SiO_2, petrol-EtOAc, 80:20) 0.21; ν_{max}($CHCl_3$, 0.025 M)/cm^{-1} 3128 (NH), 2941 (CH), 1748 (C=O), 1748 (NHC=S); δ_H(300 MHz; $CDCl_3$) 12.26 (1H, s, NH), 7.42-7.34 (5H, m, C_6H_5), 6.01 (1H, d, *J* 9.1, 5-H), 5.91 (1H, d, *J* 9.1, 4-H), 4.49 (1H, dd, *J* 4.8, 18.8, 3-NHC$H_A$$H_B$), 4.37 (1H, dd, *J* 4.4, 18.8, 3-NHC$H_A$$H_B$), 4.29 (2H, q, *J* 7.2, 3-C$H_2$$CH_3$), 3.81 (1H, dq, *J* 10.7, 7.2, 4-C$H_A$$H_B$$CH_3$), 3.62 (1H, dq, *J* 10.7, 7.2, 4-C$H_A$$H_B$$CH_3$), 1.33 (3H, t, *J* 7.2, 3-CH_2CH_3), 0.80 (3H, t, *J* 7.2, 4-CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 183.6, 178.1, 168.3, 166.2, 131.7, 130.2, 129.0, 126.9, 81.4, 69.5, 62.3, 48.9, 14.6, 13.8; *m/z* (EI) 396 (M^+, 7%), 251 (M – $C_5H_7NO_2S$, 100); (Found: MH^+, 397.0887. $C_{17}H_{21}N_2O_5S_2$ requires *M*, 397.0886).

Preparation of (4*S,5*R**)-5-(4-nitrophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-121[165] and (4*R**,5*R**)-5-(4-nitrophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-121**

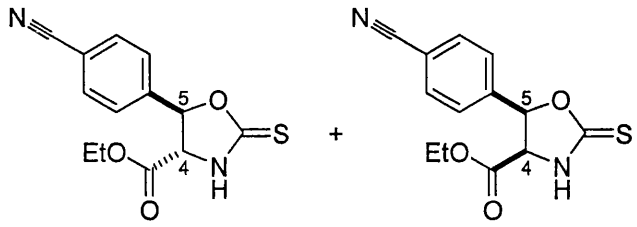


***syn*-121** ***anti*-121**

The reaction was carried out according to the typical experimental procedure III 2 with 4-nitrobenzaldehyde **37** (230 mg, 1.52 mmol). The reaction was left stirring for 25 h at 0 °C and gave in order of elution the *syn*-oxazolidinethione *syn*-**121** (199 mg, 49%) as

light yellow crystals: mp 130 °C (DCM-petrol), (lit.,[165] 124 °C); R_f(SiO_2, DCM-EtOAc, 98:2) 0.14; ν_{max}(DCM, 0.05 M)/cm^{-1} 3422 (NH), 2935 (CH), 1750 (C=O), 1609 (Ar), 1529 (Ar), 1488 (NHC=S), 1352 (CNO_2), 1171 (CO); δ_H(400 MHz; $CDCl_3$) 8.31-8.29 (2H, m, C_6H_4), 8.27 (1H, s, NH), 7.66-7.63 (2H, m, C_6H_4), 6.10 (1H, d, *J* 6.2, 5-H), 4.49 (1H, d, *J* 6.2, 4-H), 4.42-4.33 (2H, m, CH_2), 1.39 (3H, t, *J* 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 188.0, 167.1, 148.1, 142.2, 126.3, 124.1, 83.7, 64.3, 63.3, 14.1; *m/z* (EI) 296 (M^+, 100%), 223 (M – $C_3H_5O_2$, 16), 117 ($C_3H_3NO_2S$, 65), 69 (C_3H_3NO, 56), 43 (CHNO, 22), 29 (C_2H_5, 26); (Found: M^+, 296.0480. $C_{12}H_{12}N_2O_5S$ requires *M*, 296.0467) (Found: C, 48.4; H, 4.1; N, 9.4. $C_{12}H_{12}N_2O_5S$ requires C, 48.6; H, 4.08; N, 9.5%); and the *anti-oxazolidinethione anti*-**121** (85 mg, 21%) as light yellow crystals: mp 172 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.07; ν_{max}(DCM, 0.05 M)/cm^{-1} 3422 (NH), 2938 (CH), 1749 (C=O), 1608 (Ar), 1529 (Ar), 1487 (NHC=S), 1348 (NO_2), 1177 (CO); δ_H(400 MHz; $CDCl_3$) 8.28-8.24 (2H, m, C_6H_4), 7.71 (1H, s, NH), 7.57-7.54 (2H, m, C_6H_4), 6.19 (1H, d, *J* 9.8, 5-H), 5.00 (1H, d, *J* 9.8, 4-H), 3.87 (1H, dq, *J* 10.8, 7.1, CH_AH_B), 3.72 (1H, dq, *J* 10.8, 7.1, CH_AH_B), 0.89 (3H, t, *J* 7.1, CH_3); δ_C(100 MHz; $CDCl_3$) 189.5, 166.6, 148.8, 140.2, 128.1, 124.0, 83.9, 62.92, 62.86, 14.1; *m/z* (EI) 296 (M^+, 100 %), 117 ($C_3H_3NO_2S$, 58), 69 (C_3H_3NO, 50), 29 (C_2H_5, 27); (Found: M^+, 296.0472. $C_{12}H_{12}N_2O_5S$ requires *M*, 296.0467).

Preparation of (4*S,5*R**)-5-(4-cyanophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-122 and (4*R**,5*R**)-5-(4-cyanophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-122**

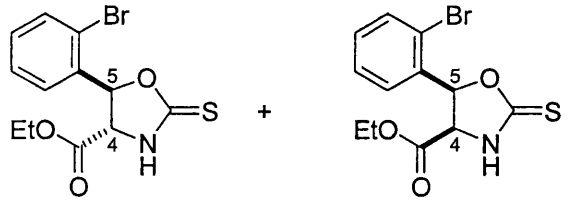


***syn*-122** ***anti*-122**

The reaction was carried out according to the typical experimental procedure III 2 with 4-cyanobenzaldehyde (199 mg, 1.52 mmol). The reaction was left stirring for 22 h at 0 °C and gave in order of elution the *syn-oxazolidinethione syn*-**122** (242 mg, 64%) as white crystals: mp 132 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.09; ν_{max}(DCM, 0.05 M)/cm^{-1} 3425 (NH), 2946 (CH), 2233 (CN), 1750 (C=O), 1613 (Ar), 1488 (NHC=S), 1171 (CO); δ_H(400 MHz; $CDCl_3$) 8.09 (1H, s, NH), 7.75-7.54 (4H, m, C_6H_4), 6.03 (1H, d, *J* 6.1, 5-H), 4.44 (1H, d, *J* 6.1, 4-H), 4.41-4.29 (2H, m, CH_2), 1.37 (3H, t, *J* 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 188.2, 167.2, 141.6, 132.8, 126.1, 117.9, 113.4, 84.0, 64.4, 63.4, 14.2; *m/z* (EI) 276 (M^+, 57%), 116 (M – C_7H_4N – CNS, 41), 69 (C_3H_3NO, 32), 29 (C_2H_5, 39); (Found: M^+, 276.0567. $C_{13}H_{12}N_2O_3S$ requires *M*, 276.0569) (Found: C, 56.6; H, 4.4; N, 10.2. $C_{13}H_{12}N_2O_3S$ requires C, 56.5; H, 4.38; N, 10.1%); and the *anti-oxazolidinethione anti*-**122** (81 mg, 21%) as white crystals: mp 169 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.06; ν_{max}(DCM, 0.05 M)/cm^{-1} 3423 (NH), 2950 (CH), 2233 (CN), 1749 (C=O), 1485 (NHC=S); δ_H(400 MHz; $CDCl_3$) 7.72-7.46 (4H, m, C_6H_4), 7.36 (1H, s, NH), 6.12 (1H, d, *J* 9.8, 5-H), 4.94 (1H, d, *J* 9.8, 4-H), 3.85 (1H, dq, *J* 10.7, 7.1, CH_AH_B), 3.72 (1H, dq, *J* 10.7, 7.1, CH_AH_B), 0.88 (3H, t, *J* 7.1, CH_3);

δ_C(100 MHz; $CDCl_3$-CD_3OD, 66:33) 189.7, 167.0, 138.9, 132.2, 127.5, 118.0, 113.1, 83.7, 63.0, 62.1, 13.6; *m/z* (EI) 276 (M^+, 98%), 102 (C_7H_6, 21), 69 (C_3H_3NO, 38), 29 (C_2H_5, 15); (Found: M^+, 276.0570. $C_{13}H_{12}N_2O_3S$ requires *M*, 276.0569).

Preparation of (4*S,5*R**)-5-(2-bromophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-123 and (4*R**,5*R**)-5-(2-bromophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-123**

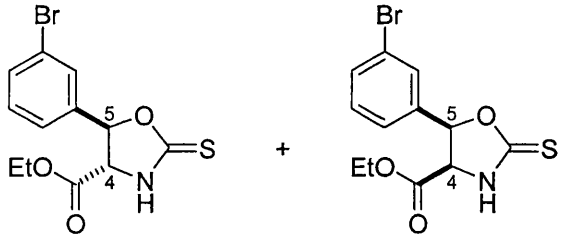


***syn*-123** ***anti*-123**

The reaction was carried out according to the typical experimental procedure III 2 with 2-bromobenzaldehyde (281 mg, 1.52 mmol). The reaction was left stirring for 23 h at 0 °C and gave in order of elution the *syn-oxazolidinethione syn*-**123** (248 mg, 55%) as white crystals: mp 103 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.22; ν_{max}(DCM, 0.05 M)/cm^{-1} 3425 (NH), 2891 (CH), 1748 (C=O), 1592 (Ar), 1571 (Ar), 1484 (NHC=S), 1174 (CO); δ_H(400 MHz; $CDCl_3$) 8.00 (1H, s, NH), 7.62-7.25 (4H, m, C_6H_4), 6.34 (1H, d, *J* 4.7, 5-H), 4.46 (1H, d, *J* 4.7, 4-H), 4.37-4.27 (2H, m, CH_2), 1.35 (3H, t, *J* 7.3, CH_3); δ_C(100 MHz; $CDCl_3$) 188.8, 167.3, 135.5, 133.3, 130.8, 128.1, 127.6, 120.9, 84.6, 64.0, 63.0, 14.2; *m/z* (EI) 331 (M + 2, 39%), 329 (M^+, 39), 117 ($C_3H_3NO_2S$, 100), 57 ($C_3H_5O_2$, 71), 43 (CHNO, 75), 29 (C_2H_5, 49); (Found: M^+, 328.9728. $C_{12}H_{12}{}^{79}BrNO_3S$ requires *M*, 328.9721) (Found: C, 43.7; H, 3.7; N, 4.2. $C_{12}H_{12}BrNO_3S$ requires C, 43.7; H, 3.65; N, 4.2%); and the *anti-oxazolidinethione anti*-**123** (134 mg, 29%) as white crystals: mp 144 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.13;

ν_{max}(DCM, 0.05 M)/cm^{-1} 3424 (NH), 2950 (CH), 1747 (C=O), 1484 (NHC=S), 1178 (CO); δ_H(400 MHz; $CDCl_3$) 7.58-7.23 (5H, m, C_6H_4 and NH), 6.41 (1H, d, *J* 9.2, 5-H), 5.00 (1H, d, *J* 9.2, 4-H), 3.80 (1H, dq, *J* 10.7, 7.2, CH_AH_B), 3.66 (1H, dq, *J* 10.7, 7.2, CH_AH_B), 0.82 (3H, t, *J* 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 189.8, 166.9, 132.6, 132.3, 130.7, 127.8, 127.7, 122.1, 84.5, 62.2, 61.2, 13.6; *m/z* (EI) 331 (M + 2, 29%), 329 (M^+, 29), 258 (M – $C_3H_5O_2$ + 2, 14), 256 (M – $C_3H_5O_2$, 14), 117 ($C_3H_3NO_2S$, 100), 43 (CHNO, 43), 29 (C_2H_5, 65); (Found: M^+, 328.9726. $C_{12}H_{12}{}^{79}BrNO_3S$ requires *M*, 328.9721).

Preparation of (4*S,5*R**)-5-(3-bromophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-124 and (4*R**,5*R**)-5-(3-bromophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-124**

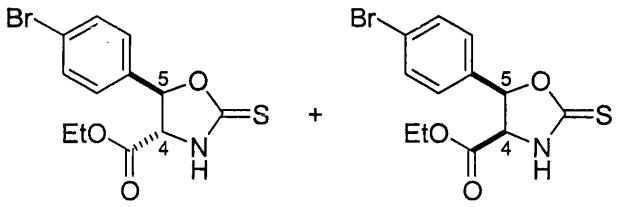


***syn*-124** ***anti*-124**

The reaction was carried out according to the typical experimental procedure III 2 with 3-bromobenzaldehyde (281 mg, 1.52 mmol). The reaction was left stirring for 21 h at 0 °C and gave in order of elution the *syn-oxazolidinethione syn*-**124** (260 mg, 57%) as white crystals: mp 83 °C (DCM-petroleum spirit 40-60 °C); R_f(SiO_2, DCM-EtOAc, 98:2) 0.26; ν_{max}(DCM, 0.05 M)/cm^{-1} 3424 (NH), 2913 (CH), 1749 (C=O), 1599 (Ar), 1574 (Ar), 1487 (NHC=S), 1177 (CO); δ_H(400 MHz; $CDCl_3$) 7.78 (1H, s, NH), 7.57-7.53 (2H, m, C_6H_4), 7.37-7.29 (2H, m, C_6H_4), 5.94 (1H, d, *J* 6.2, 5-H), 4.45 (1H, d, *J*

6.2, 4-H), 4.41-4.28 (2H, m, CH_2), 1.36 (3H, t, *J* 7.0, CH_3); δ_C(100 MHz; $CDCl_3$) 188.7, 167.7, 139.1, 132.9, 131.0, 128.8, 124.4, 123.4, 84.8, 64.8, 63.6, 14.6; *m/z* (EI) 331 (M + 2, 26%), 329 (M^+, 26), 117 ($C_3H_3NO_2S$, 86), 44 (CO_2, 100), 29 (C_2H_5, 89); (Found: M^+, 328.9729. $C_{12}H_{12}{}^{79}BrNO_3S$ requires *M*, 328.9721) (Found: C, 43.7; H, 3.7; N, 4.4. $C_{12}H_{12}BrNO_3S$ requires C, 43.7; H, 3.65; N, 4.2%); and the *anti-oxazolidinethione anti-***124** (140 mg, 31%) as white crystals: mp 129 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.14; ν_{max}(DCM, 0.05 M)/cm^{-1} 3424 (NH), 2935 (CH), 1749 (C=O), 1599 (Ar), 1573 (Ar), 1489 (NHC=S), 1179 (CO); δ_H(400 MHz; $CDCl_3$) 7.54-7.47 (3H, m, C_6H_4 and NH), 7.29-7.27 (2H, m, C_6H_4), 6.04 (1H, d, *J* 9.8, 5-H), 4.91 (1H, d, *J* 9.8, 4-H), 3.86 (1H, dq, *J* 10.8, 7.2, CH_AH_B), 3.76 (1H, dq, *J* 10.8, 7.2, CH_AH_B), 0.90 (3H, t, *J* 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 189.8, 166.8, 135.5, 133.0, 130.5, 130.0, 125.5, 122.8, 84.4, 62.9, 62.8, 14.0; *m/z* (EI) 331 (M + 2, 24%), 329 (M^+, 23), 117 ($C_3H_3NO_2S$, 52), 57 ($C_3H_5O_2$, 70), 43 (CHNO, 100), 29 (C_2H_5, 83); (Found: M^+, 328.9726. $C_{12}H_{12}{}^{79}BrNO_3S$ requires *M*, 328.9721) (Found: C, 43.7; H, 3.6; N, 4.3. $C_{12}H_{12}BrNO_3S$ requires C, 43.7; H, 3.65; N, 4.2%).

Preparation of (4*S,5*R**)-5-(4-bromophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-125 and (4*R**,5*R**)-5-(4-bromophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-125**

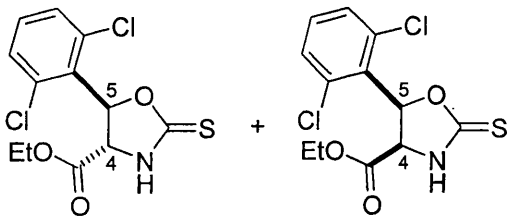


***syn*-125** ***anti*-125**

The reaction was carried out according to the typical experimental procedure III 2 with 4-bromobenzaldehyde (281 mg, 1.52 mmol). The reaction was left stirring for 21 h at 0 °C and gave in order of elution the *syn-oxazolidinethione syn*-**125** (283 mg, 62%) as white crystals: mp 112 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.23; ν_{max}(DCM, 0.05 M)/cm^{-1} 3424 (NH), 2935 (CH), 1750 (C=O), 1596 (Ar), 1490 (NHC=S), 1174 (CO); δ_H(400 MHz; $CDCl_3$) 7.95 (1H, s, NH), 7.58-7.55 (2H, m, C_6H_4), 7.31-7.26 (2H, m, C_6H_4), 5.93 (1H, d, *J* 6.2, 5-H), 4.43 (1H, d, *J* 6.2, 4-H), 4.39-4.27 (2H, m, CH_2), 1.35 (3H, t, *J* 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 188.4, 167.5, 135.6, 132.2, 127.2, 123.6, 84.8, 64.5, 63.2, 14.2; *m/z* (EI) 331 (M + 2, 22%), 329 (M^+, 22), 57 ($C_3H_5O_2$, 45), 43 (CHNO, 100), 29 (C_2H_5, 83); (Found: M^+, 328.9733. $C_{12}H_{12}{}^{79}BrNO_3S$ requires *M*, 328.9721) (Found: C, 43.6; H, 3.6; N, 4.3. $C_{12}H_{12}BrNO_3S$ requires C, 43.7; H, 3.65; N, 4.2%); and the *anti-oxazolidinethione anti*-**125** (121 mg, 27%) as white crystals: mp 122 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.11; ν_{max}(DCM, 0.05 M)/cm^{-1} 3424 (NH), 2935 (CH), 1749 (C=O), 1595 (Ar), 1492 (NHC=S); δ_H(400 MHz; $CDCl_3$) 7.58 (1H, s, NH), 7.53-7.50 (2H, m, C_6H_4), 7.23-7.18 (2H, m, C_6H_4), 6.04 (1H, d, *J* 9.8, 5-H), 4.90 (1H, d, *J* 9.8, 4-H), 3.85 (1H, dq, *J* 10.8, 7.2, CH_AH_B), 3.74 (1H, dq, *J* 10.8,

7.2, CH_AH_B), 0.89 (3H, t, *J* 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 189.8, 166.9, 132.4, 132.0, 128.6, 124.2, 84.7, 62.9, 62.7, 14.0; *m/z* (EI) 331 (M + 2, 37%), 329 (M^+, 37), 273 (M – $C_3H_6O_2$ + 2, 9), 271 (M – $C_3H_6O_2$, 9), 117 ($C_3H_3NO_2S$, 100), 44 (CO_2, 54), 29 (C_2H_5, 83); (Found: M^+, 328.9707. $C_{12}H_{12}{}^{79}BrNO_3S$ requires *M*, 328.9721).

Preparation of (4*S,5*R**)-5-(2,6-dichlorophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-126 and (4*R**,5*R**)-5-(2,6-dichlorophenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-126**

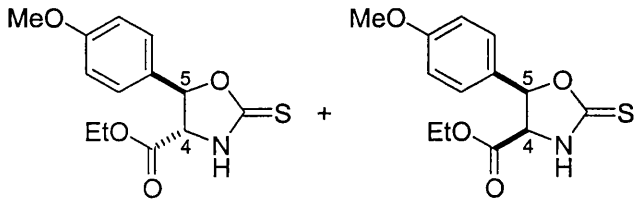


***syn*-126** ***anti*-126**

The reaction was carried out according to the typical experimental procedure III 2 with 2,6-dichlorobenzaldehyde (266 mg, 1.52 mmol). The reaction was left stirring for 25 h at 0 °C and gave in order of elution the *syn-oxazolidinethione syn*-**126** (152 mg, 34%) as white crystals: mp 222 °C ($CHCl_3$); R_f(SiO_2, DCM-EtOAc, 98:2) 0.17; ν_{max}(1% in KBr)/cm^{-1} 3156 (NH), 2994 (CH), 1759 (C=O), 1583 (Ar), 1566 (Ar), 1519 (NHC=S), 1172 (CO); δ_H(400 MHz; $CDCl_3$) 10.93 (1H, s, NH), 7.63-7.50 (3H, m, $C_6H_3Cl_2$), 6.56 (1H, d, *J* 8.4, 5-H), 4.92 (1H, d, *J* 8.4, 4-H), 4.42 (1H, dq, *J* 10.7, 7.1, CH_AH_B), 4.15 (1H, dq, *J* 10.7, 7.1, CH_AH_B), 1.21 (3H, t, *J* 7.1, CH_3); δ_C(100 MHz; DMSO) 188.2, 168.6, 135.9, 133.1, 130.6, 80.6, 62.7, 14.8; *m/z* (EI) 323 (M + 4, 12%), 321 (M + 2, 66), 319 (M^+, 100); (Found: M^+, 318.9828. $C_{12}H_{11}Cl_2NO_3S$ requires *M*, 318.9837) (Found: C, 45.1; H, 3.4; N, 4.4. $C_{12}H_{11}{}^{35}Cl_2NO_3S$ requires C, 45.0; H, 3.46; N, 4.4%);

and the *anti-oxazolidinethione anti*-**126** (65 mg, 15%) as white crystals: mp 162 °C (DCM); R_f(SiO_2, DCM-EtOAc, 98:2) 0.11; ν_{max}($CHCl_3$, 0.05 M)/cm^{-1} 3439 (NH), 2991 (CH), 1749 (C=O), 1583 (Ar), 1566 (Ar), 1489 (NHC=S); δ_H(300 MHz; $CDCl_3$) 7.56 (1H, s, NH), 7.40-7.25 (3H, m, $C_6H_3Cl_2$), 6.89 (1H, d, *J* 11.5, 5-H), 4.95 (1H, d, *J* 11.5, 4-H), 4.03-3.85 (2H, m, CH_2), 0.92 (3H, t, *J* 7.2, CH_3); δ_C(75 MHz; $CDCl_3$) 189.6, 166.9, 136.2, 131.4, 129.3, 81.2, 63.0, 60.1, 13.8; *m/z* (EI) 323 (M + 4, 14%), 321 (M + 2, 73), 319 (M^+, 100); (Found: MH^+, 319.9909. $C_{12}H_{12}{}^{35}Cl_2NO_3S$ requires *M*, 319.9909).

Preparation of (4*S,5*R**)-5-(4-methoxyphenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-127 and (4*R**,5*R**)-5-(4-methoxyphenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-127**

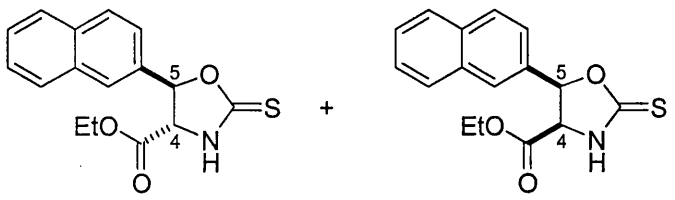


***syn*-127** ***anti*-127**

The reaction was carried out according to the typical experimental procedure III 2 with 4-anisaldehyde (185 μL, 1.52 mmol). The reaction was left stirring for 23 h at 0 °C and gave in order of elution the *syn-oxazolidinethione syn*-**127** (170 mg, 44%) as white crystals: mp 80 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.19; ν_{max}(DCM, 0.05 M)/cm^{-1} 3426 (NH), 2815 (CH), 1748 (C=O), 1614 (Ar), 1517 (Ar), 1486 (NHC=S), 1171 (CO), 1032 (CO); δ_H(400 MHz; $CDCl_3$) 7.71 (1H, s, NH), 7.34-7.32 (2H, m, C_6H_4), 6.96-6.92 (2H, m, C_6H_4), 5.90 (1H, d, *J* 6.2, 5-H), 4.47 (1H, d, *J* 6.2, **4**-H), 4.37-

4.25 (2H, m, CH_2), 3.82 (1H, s, OCH_3), 1.34 (3H, t, *J* 7.0, OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 188.7, 167.7, 160.4, 128.5, 127.3, 114.4, 85.8, 64.4, 62.9, 55.4, 14.2; *m/z* (EI) 281 (M^+, 70%), 57 (C_3H_5O, 20), 43 (CHNO, 23), 29 (C_2H_5, 25); (Found: M^+, 281.0725. $C_{13}H_{15}NO_4S$ requires *M*, 281.0722); and the *anti-oxazolidinethione anti*-**127** (92 mg, 23%) as white crystals: mp 87 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.11; ν_{max}(DCM, 0.05 M)/cm^{-1} 3425 (NH), 2859 (CH), 1747 (C=O), 1614 (Ar), 1517 (Ar), 1487 (NHC=S), 1171 (CO), 1032 (CO); δ_H(400 MHz; $CDCl_3$) 7.51 (1H, s, NH), 7.25-7.21 (2H, m, C_6H_4), 6.90-6.86 (2H, m, C_6H_4), 6.04 (1H, d, *J* 9.8, 5-H), 4.86 (1H, d, *J* 9.8, 4-H), 3.84 (1H, dq, *J* 10.6, 7.2, CH_AH_B), 3.80 (3H, s, OCH_3), 3.73 (1H, dq, *J* 10.6, 7.2, CH_AH_B), 0.88 (3H, t, *J* 7.2, OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 189.9, 167.1, 160.7, 128.3, 125.4, 114.1, 85.5, 63.0, 62.5, 55.7, 14.0; *m/z* (EI) 281 (M^+, 28%), 69 (C_3H_3NO, 67), 43 (CHNO, 100), 29 (C_2H_5, 42); (Found: M^+, 281.0720. $C_{13}H_{15}NO_4S$ requires *M*, 281.0722).

Preparation of (4*S,5*R**)-5-(2-naphthyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-128 and (4*R**,5*R**)-5-(2-naphthyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-128**

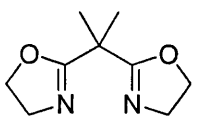


***syn*-128** ***anti*-128**

The reaction was carried out according to the typical experimental procedure III 2 with 2-naphthaldehyde (237 mg, 1.52 mmol). The reaction was left stirring for 21 h at 0 °C

and gave in order of elution the *syn-oxazolidinethione syn*-**128** (221 mg, 53%) as white crystals: mp 145 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.21; ν_{max}(DCM, 0.05 M)/cm^{-1} 3426 (NH), 2957 (CH), 1749 (C=O), 1582 (Ar), 1487 (NHC=S), 1180 (CO); δ_H(400 MHz; $CDCl_3$) 7.92-7.85 (5H, m, $C_{10}H_7$ and NH), 7.55-7.53 (2H, m, $C_{10}H_7$), 7.48-7.46 (1H, m, $C_{10}H_7$), 6.14 (1H, d, *J* 6.2, 5-H), 4.56 (1H, d, *J* 6.2, 4-H), 4.42-4.29 (2H, m, CH_2), 1.38 (3H, t, *J* 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 189.1, 168.1, 134.1, 133.8, 133.1, 129.7, 128.5, 128.0, 127.3, 127.1, 125.6, 122.6, 86.1, 64.9, 63.4, 14.6; *m/z* (EI) 301 (M^+, 75%), 256 (M – C_2H_5O, 7), 127 ($C_{10}H_7$, 26), 69 (C_3H_3NO, 70), 43 (CHNO, 43), 29 (C_2H_5, 50); (Found: M^+, 301.0760. $C_{16}H_{15}NO_3S$ requires *M*, 301.0773); and the *anti-oxazolidinethione anti*-**128** (147 mg, 36%) as white crystals mp 169 °C (DCM-petrol); R_f(SiO_2, DCM-EtOAc, 98:2) 0.11; ν_{max}(DCM, 0.05 M)/cm^{-1} 3425 (NH), 2913 (CH), 1748 (C=O), 1603 (Ar), 1489 (NHC=S), 1175 (CO); δ_H(400 MHz; $CDCl_3$) 7.86-7.83 (4H, m, $C_{10}H_7$), 7.55-7.50 (3H, m, $C_{10}H_7$ and NH), 7.39-7.36 (1H, m, $C_{10}H_7$), 6.26 (1H, d, *J* 9.8, 5-H), 4.97 (1H, d, *J* 9.8, 4-H), 3.64 (1H, dq, *J* 10.7, 7.2, CH_AH_B), 3.48 (1H, dq, *J* 10.7, 7.2, CH_AH_B), 0.55 (3H, t, *J* 7.2, CH_3); δ_C(100 MHz; $CDCl_3$) 189.7, 166.7, 133.5, 132.5, 130.3, 128.4, 128.1, 127.6, 126.9, 126.7, 126.4, 123.3, 85.4, 62.8, 62.2, 13.4; *m/z* (EI) 301 (M^+, 68%), 256 (M – C_2H_5O, 8), 127 ($C_{10}H_7$, 28), 43 (CHNO, 57), 29 (C_2H_5, 77); (Found: M^+, 301.0763. $C_{16}H_{15}NO_3S$ requires *M*, 301.0773).

Preparation of 2,2'-isopropylidenebis-(2-oxazoline) 129

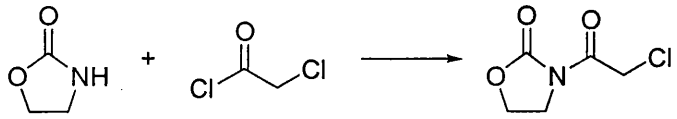


Ethanolamine (0.33 mL, 5.49 mmol) was added dropwise to a solution of dimethylmalononitrile (0.21 g, 2.20 mmol), and $Cd(OAc)_2(H_2O)_2$ (29 mg, 0.11 mmol)

in chlorobenzene (6 mL). A reflux was maintained for 24 h and the reaction was cooled and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, MeOH-DCM, 5:95) to yield the *bisoxazoline* **129** (217 mg, 54%), as a colourless oil; R_f(SiO_2, DCM-MeOH, 95:5) 0.14; ν_{max}(DCM, 0.05 M)/cm^{-1} 2984 (CH), 2944 (CH), 2908 (CH), 2886 (CH), 1659 (C=N); δ_H(400 MHz; $CDCl_3$) 4.30 (2H, t, *J* 9.5 ,O-CH_2), 3.88 (2H, t, *J* 9.5, N-CH_2), 1.53 (6H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 169.6, 68.0, 54.4, 38.6, 24.3; *m/z* (EI) 182 (M^+, 6%), 163 (M – Me, 52), 112 (M – C_3H_4NO, 38), 41 (C_3H_5, 100); (Found: M^+, 182.1058. $C_9H_{14}N_2O_2$ requires *M*, 182.1055).

III 3 Preparation of 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one 116

Preparation of 3-(2-chloroacetyl)-oxazolidin-2-one 141



139 **140** **141**

A solution of BuLi (2.5 M in hexane, 8.0 mL, 20.0 mmol) was added dropwise to a solution of oxazolidine-2-one **139** (1.74 g, 20.0 mmol) in dry THF (300 mL) at -78 °C and the reaction was stirred for an additional 15 min. The temperature was allowed to reach RT for 2.5 h and then the mixture was cooled to -78 °C for 15 min. Chloroacetyl chloride **140** (1.75 mL, 22.0 mmol) was added slowly to the reaction mixture. After 15 min, the light yellow solution was warmed to RT for a further 30 min. The reaction was quenched with sat. aqueous ammonium chloride solution (10 mL). The mixture was

concentrated under reduced pressure, taken up in water (10 mL) and extracted with DCM (3 × 40 mL). The organic portions were dried ($MgSO_4$) and concentrated under reduced pressure. The *chloroimide* **141** (3.14 g, 96%) was obtained as a white powder. An analytical sample was prepared by recrystallization from DCM; mp 61 °C (DCM); R_f(SiO_2, DCM) 0.19; ν_{max}(DCM, 0.05 M)/cm^{-1} 2966 (CH), 2928 (CH), 1782 (C=O), 1720 (C=O); δ_H(400 MHz; $CDCl_3$) 4.74 (2H, s, CH_2Cl), 4.51 (2H, t, *J* 8.0, CH_2), 4.09 (2H, t, *J* 8.0, CH_2); δ_C(100 MHz; $CDCl_3$) 165.7, 152.9, 62.7, 43.3, 42.5; *m/z* (EI) 165 (M + 2, 13%), 163 (M^+, 43), 79 ($C_2H_2{}^{37}ClO$, 17), 77 ($C_2H_2{}^{35}ClO$, 55), 70 (C_3H_4NO, 70), 44 (CO_2, 91), 42 (C_2H_4N, 100); (Found: M^+, 163.0038. $C_5H_6{}^{35}ClNO_3$ requires *M*, 163.0036) (Found: C, 36.7; H, 3.7; N, 8.5. $C_5H_6ClNO_3$ requires C, 36.7; H, 3.70; N, 8.6%).

Preparation of 3-(2-azidoacetyl)-oxazolidin-2-one 142

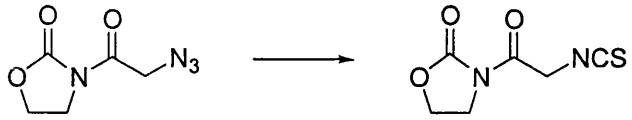
Danger, might be explosive at high temperatures!

141 **142**

A solution of sodium azide (6.50 g, 100 mmol) in water (20 mL) was added to a solution of **135** (3.14 g, 19.2 mmol) in DCM (20 mL). This biphasic system was stirred vigorously and tetrabutylammonium hydrogen sulphate (0.68 g, 2.00 mmol) was added. After 1.5 h at RT, the organic layer was separated and concentrated under reduced pressure. The residue was filtered through silica using DCM as the mobile phase. After concentration, the *azidoimide* **136** (2.70 g, 83%) was obtained as a colourless oil; R_f(SiO_2, DCM) 0.18; ν_{max}(DCM, 0.05 M)/cm^{-1} 2926 (CH), 2210 (N_3), 1786 (C=O),

1714 (C=O); δ_H(400 MHz; $CDCl_3$) 4.52 (2H, t, *J* 8.1, CH_2), 4.51 (2H, s, CH_2N_3), 4.09 (2H, t, *J* 8.1, CH_2); δ_C(100 MHz; $CDCl_3$) 167.5, 153.0, 62.9, 52.3, 42.1.

Preparation of 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one 116



142 **116**

Triphenylphosphine (7.71 g, 29.3 mmol) was added to a solution of **142** (4.53 g, 26.7 mmol) in THF (30 mL) and CS_2 (30 mL) in a 1 L round bottom flask fitted with a condenser. After evolution of nitrogen, the solution gently self-refluxed and was left overnight. After concentration under reduced pressure, the residue was purified by flash chromatography (SiO_2, DCM) to yield the *isothiocyanatoimide* **116** (3.00 g, 60%), as a white solid which was recrystallised in DCM-hexane; mp 99 °C (DCM-hexane); R_f(SiO_2, DCM) 0.26; ν_{max}(DCM, 0.05 M)/cm^{-1} 2928 (CH), 2064 (NCS), 1786 (C=O), 1721 (C=O); δ_H(400 MHz; $CDCl_3$) 4.85 (2H, s, CH_2NCS), 4.54 (2H, t, *J* 8.1, CH_2), 4.11 (2H, t, *J* 8.1, CH_2); δ_C(100 MHz; $CDCl_3$) 165.7, 153.4, 140.0, 63.6, 49.6, 42.8; *m/z* (EI) 186 (M^+, 100%); (Found: M^+, 186.0099. $C_6H_6N_2O_3S$ requires *M*, 186.0099) (Found: C, 38.7; H, 3.3; N, 15.1. $C_6H_6N_2O_3S$ requires C, 38.7; H, 3.25; N, 15.1%).

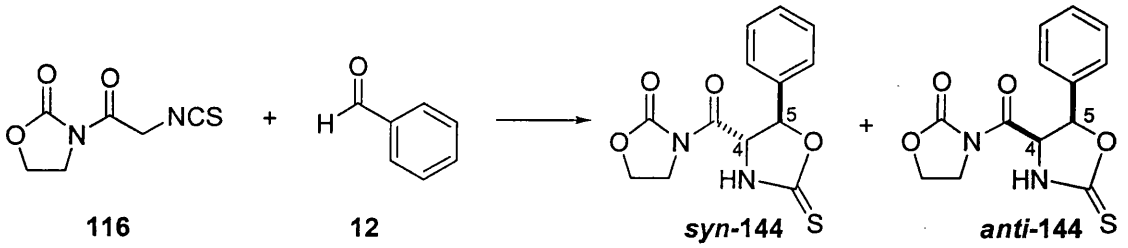
Isolation of 3-(2-triphenylphosphazoacetyl)-oxazolidin-2-one 143

142 **143**

Triphenylphosphine (362 mg, 1.38 mmol) was added to a solution of **142** (235 mg, 1.38 mmol) in dry THF (5 mL) at RT, under nitrogen. After evolution of nitrogen (2 h), the solution *phosphazoimide* **143**, generated *in situ*, was cooled to -78 °C and transferred to a solution of $Mg(ClO_4)_2$ (31 mg, 0.14 mmol), bipyridine (22 mg, 0.14 mmol), benzaldehyde **12** (150 μL, 1.52 mmol) and triethylamine (39μL, 0.28 mmol) in dry THF at -78 °C under nitrogen. No aldol reaction occurred but the phosphazoimide **143** crashed out of the solution after 2 h. The reaction was quenched with sat. aqueous ammonium chloride solution (5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The organic portions were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The white solid was recrystallised from DCM to yield a white powder of phosphazoimide **143** (57 mg, 10%); mp 153 °C (DCM); ν_{max}(1% in KBr)/cm^{-1} 3013 (CH), 2819 (CH), 2694 (CH), 1761 (C=O), 1712 (C=O), 1587 (Ar), 1438 (P-Ar); δ_H(400 MHz; DMSO) 7.92-7.74 (15H, m, C_6H_5), 4.36 (2H, t, *J* 8.0, CH_2), 4.31 (1H, d, *J* 6.6, CH_AH_BNP), 4.28 (1H, d, *J* 6.6, CH_AH_BNP), 3.77 (2H, t, *J* 8.0, CH_2); δ_C(100 MHz; DMSO) 169.9, 154.2, 135.6, 134.3, 134.2, 130.6,130.5, 122.2, 121.2, 64.1, 45.8, 43.1; δ_P(122 MHz; DMSO) 40.3; *m/z* (FAB) 405 (M + H, 100%), 262 (PPh_3, 6); (Found: MH^+, 405.1372. $C_{23}H_{21}N_2O_3P$ requires *M*, 405.1368).

III 4 Use of 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one 116 for the development of asymmetric catalysis

Preparation of 3-((4*S,5*R**)-5-phenyl-2-thioxo-oxazolidine-4-carbonyl)-oxazolidin-2-one *syn*-144 and 3-((4*R**,5*R**)-5-phenyl-2-thioxo-oxazolidine-4-carbonyl)-oxazolidin-2-one *anti*-144**

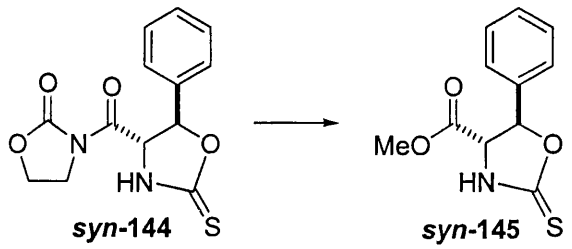


A mixture of $Mg(ClO_4)_2$ (120 mg, 0.54 mmol), 2,2'-bipyridine (85 mg, 0.54 mmol) and 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one **116** (1.00 g, 5.37 mmol) in dry THF (20 mL) was stirred for 15 min under nitrogen at 0 °C. Triethylamine (150 μL, 1.07 mmol) was added and 5 min later, benzaldehyde **12** (0.60 mL, 5.91 mmol) was introduced. A precipitation appeared. Forty min latter the reaction was completed (TLC) and quenched with sat. aqueous ammonium chloride solution (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 40 mL). The organic portions were combined and washed with $CuSO_4$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM-EtOAc, 98:2 then 90:10 and finally 80:20) to give in order of elution the *syn-oxazolidinethione syn*-**144** (1.00 g, 64%), as white crystals: mp 177 °C (DCM-hexane); R_f(SiO_2, DCM-EtOAc, 98:2) 0.08; ν_{max}(1% in KBr)/cm^{-1} 3174 (NH), 2996 (CH), 1767 (C=O), 1688 (C=O), 1594 (Ar), 1520 (NHC=S), 1 168 (CO);

δ_H(400 MHz; DMSO) 10.48 (1H, s, NH), 7.47-7.36 (5H, m, C_6H_5), 6.08 (1H, d, *J* 2.7, 5-H), 5.47 (1H, d, *J* 2.7, 4-H), 4.46 (2H, m, CH_2), 3.95 (2H, m, CH_2); δ_C(100 MHz; DMSO) 188.8, 168.0, 153.4, 137.7, 128.8, 128.5, 126.1, 84.2, 63.4, 62.9, 42.6; *m/z* (EI) 292 (M^+, 17%), 117 ($C_3H_3NO_2S$, 100), 90 (C_7H_6, 63), 77 (C_6H_5, 49), 42 (CNO, 43); (Found: M^+, 292.0521. $C_{13}H_{12}N_2O_4S$ requires *M*, 292.0518); and the *anti-oxazolidinethione anti*-**144** (0.150 g, 9%), as white crystals: mp 189 °C (DCM); R_f(SiO_2, DCM-EtOAc, 90:10) 0.06; ν_{max}(1% in KBr)/cm^{-1} 3317 (NH), 3051 (CH), 1775 (C=O), 1690 (C=O), 1509 (NHC=S), 1173 (CO); δ_H(400 MHz; DMSO) 10.51 (1H, s, NH), 7.42-7.36 (3H, m, C_6H_5), 7.16-7.12 (2H, m, C_6H_5), 6.23 (1H, d, *J* 10.0, 5-H), 5.89 (1H, d, *J* 10.0, 4-H), 4.21 (1H, app. dt, *J* 9.2, 6.6, CH_AH_B), 3.80 (1H, app. dt, *J* 9.2, 6.6, CH_AH_B), 3.68 (1H, ddd, *J* 10.4, 9.2, 6.6, CH_CH_D), 2.95 (1H, ddd, *J* 10.4, 9.2, 6.6, CH_CH_D); δ_C(100 MHz; DMSO) 189.0, 167.7, 153.4, 134.5, 130.2, 128.9, 127.6, 84.6, 63.9, 63.3, 42.9; *m/z* (EI) 292 (M^+, 10%), 86 ($C_3H_4NO_2$, 24), 77 (C_6H_5, 17), 44 (CO_2, 35); (Found: M^+, 292.0521. $C_{13}H_{12}N_2O_4S$ requires *M*, 292.0518).

The enantiomers of *syn*-**144** were separated analytically by chiral HPLC using the conditions in the general information section; tr_1 = 83.0 min and tr_2 = 160.9 min. The enantiomers of *anti*-**144** could not be separated analytically by chiral HPLC; Using the conditions in the general information section tr = 56.3 min.

(4*S,5*R**)-5-Phenyl-2-thioxo-oxazolidine-4-carboxylic acid methyl ester *syn*-145**

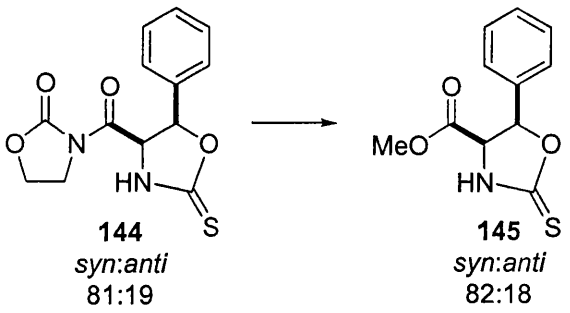


syn-144 *syn*-145

A solution of methyl magnesium bromide (3M in ether, 0.26 mL, 0.77 mmol) in methanol (2 mL) at 0 °C was added by cannula transfer to a solution of the oxazolidinethione *syn*-**144** (204 mg, 0.70 mmol) dissolved in dry THF (5 mL) and cooled to 0 °C. Three min later, the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (5 mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1N, 10 mL) and DCM (15 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 20 mL). The organic portions were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM-EtOAc, 98:2) to give the *oxazolidinethione syn*-**145** (111 mg, 67%), as white crystals; mp 101 °C (DCM); R_f(SiO_2, DCM-EtOAc, 98:2) 0.21; ν_{max}(DCM, 0.05 M)/cm^{-1} 3426 (NH), 1755 (C=O), 1488 (NHC=S), 1174 (CO); δ_H(400 MHz; $CDCl_3$) 7.95 (1H, s, NH), 7.47-7.38 (5H, m, C_6H_5), 5.98 (1H, d, *J* 5.9, 5-H), 4.52 (1H, d, *J* 5.9, 4-H), 3.88 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 188.5, 168.1, 136.4, 129.3, 128.9, 125.3, 85.4, 64.3, 53.4; *m/z* (EI) 237 (M^+, 89%), 117 ($C_3H_3NO_2S$, 100), 77 (C_6H_5, 92), 43 (CHNO, 37); (Found: M^+, 237.0461. $C_{11}H_{11}NO_3S$ requires *M*, 237.0460) (Found: C, 55.6; H 4.6; N, 5.9). $C_{11}H_{11}NO_3S$ requires C, 55.7; H, 4.67; N, 5.9%).

The enantiomers of *syn*-**145** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 9.5 min and tr_2 = 11.0 min.

(4*R,5*R**)-5-Phenyl-2-thioxo-oxazolidine-4-carboxylic acid methyl ester *anti*-145**



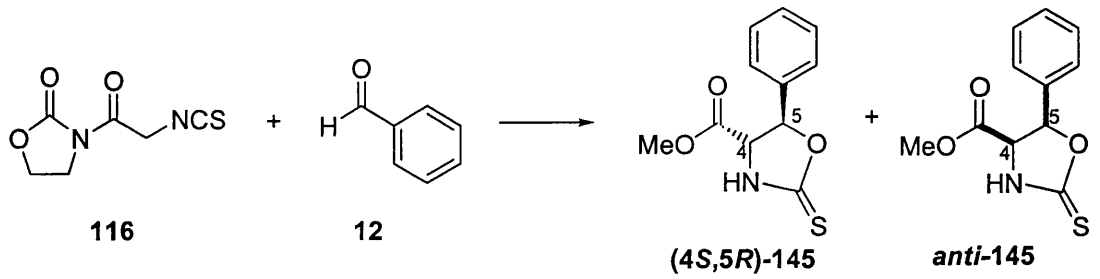
144
syn:*anti*
81:19

145
syn:*anti*
82:18

A solution of methyl magnesium bromide (3M in ether, 0.60 mL, 1.77 mmol) in methanol (6.5 mL) at 0 °C was added by cannula transfer to a solution of the diastereomeric mixture of **144** (403 mg, 1.38 mmol, *syn*:*anti* = 81:19), dissolved in dry THF (20 mL) and cooled to 0 °C. Three min later, the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (20 mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1N, 20 mL) and DCM (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 20 mL). The organic portions were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM-EtOAc, 98:2) to give the *syn*- and *anti-oxazolidinethiones*, **145** (220 mg, 67%, *syn*:*anti* = 82:18), as white needles. Analytical samples of *anti*-**145** were prepared by recrystallization from DCM-hexane; mp 124 °C (DCM-hexane); R_f(SiO_2, DCM-EtOAc, 98:2) 0.15; ν_{max}(DCM, 0.05 M)/cm^{-1} 3426 (NH), 1754 (C=O), 1486 (NHC=S), 1176 (CO); δ_H(400 MHz; $CDCl_3$) 7.39-7.28 (5H, m, C_6H_5), 6.10 (1H, d, *J* 9.8, 5-H), 4.95 (1H, d, *J* 9.8, 4-H), 3.27 (3H, s, CH_3); δ_C(100 MHz; $CDCl_3$) 190.1, 167.7, 133.2, 129.9, 128.8, 126.7, 85.5, 63.3, 52.9; *m/z* (EI) 237 (M^+, 44%), 117 ($C_3H_3NO_2S$, 70), 77 (C_6H_5, 100), 59 (CHNS, 39); (Found: M^+, 237.0458. $C_{11}H_{11}NO_3S$ requires *M*, 237.0460) (Found: C, 55.7; H 4.6; N, 5.8. $C_{11}H_{11}NO_3S$ requires C, 55.7; H, 4.67; N, 5.9%).

The enantiomers of *anti*-**145** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 13.8 min and tr_2 = 38.8 min.

Preparation of (4*S*,5*R*)- and *anti*-oxazolidinethiones (4*S*,5*R*)- and *anti*-145; serving as a typical experimental procedure for the development of asymmetric catalysis



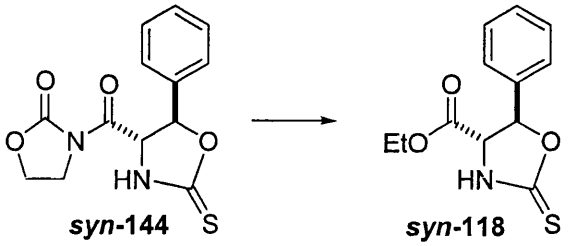
116 **12** **(4*S*,5*R*)-145** ***anti*-145**

A mixture of $Mg(ClO_4)_2$ (15 mg, 0.07 mmol), [*R*-(*R**,*R**)]-2,6-bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine **136** (28 mg, 0.08 mmol) and 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one **116** (128 mg, 0.69 mmol) was stirred for 1 h in dry DCM (15 mL) with activated powdered 4 Å MS (200 mg) under nitrogen at RT. The temperature was then lowered to -78 °C. After 15 min, benzaldehyde **12** (77 μL, 0.76 mmol) and diisopropylethylamine (24 μL, 0.14 mmol) were added and the mixture was stirred for a further 23 h at -78 °C. The reaction was quenched with sat. aqueous ammonium chloride solution (5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in dry THF (15 mL) and cooled to 0 °C. A solution of methyl magnesium bromide (3M in ether, 0.30 mL, 0.89 mmol) in methanol (5 mL) at 0 °C was added to the previous solution by cannula transfer. Three min later, the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (5 mL). The mixture was concentrated

under reduced pressure, taken up in aqueous HCl (1N, 10 mL) and DCM (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The organic portions were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc-DCM, 2:98) to give a mixture of the *syn*- and *anti*-oxazolidinethiones **145** (141 mg, 86%, *syn*:*anti* = 78:22, ee_{syn} = 90% $[\alpha]_D^{21}$ = +30.2° (*c* = 3.4, DCM), ee_{trans} = 85% $[\alpha]_D^{21}$ = +123.6° (*c* = 0.3, DCM)), as white solids. Data identical to those reported earlier.

The same reaction with isolation of the intermediate (4*S*,5*R*)-**144** by column chromatography and two consecutive recrystallizations from DCM-hexane furnished long flat colourless prisms used for X-ray experiment (Appendix B) ($[\alpha]_D^{21}$ = +41.8° (*c* = 1.7, THF)). The methanolysis of these crystals of (4*S*,5*R*)-**144**, following the procedure aforementioned, formed the ester (4*S*,5*R*)-**145** in 99.9% ee (tr_2 = 13.6 min using the standard HPLC conditions section III 1, see appendix D for chromatogram), $[\alpha]_D^{21}$ = +27.8° (*c* = 0.53, DCM), major enantiomer obtained in the asymmetric catalysis.

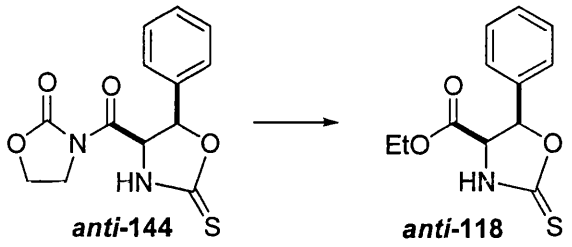
(4*S,5*R**)-5-Phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *syn*-118**



***syn*-144** ***syn*-118**

A solution of methyl magnesium bromide (3M in ether, 0.51 mL, 1.52 mmol) in ethanol (5.6 mL) at 0 °C was added *via* cannula transfer to a suspension of the *syn*-oxazolidinethione *syn*-144 (403 mg, 1.38 mmol, de = 99%) dissolved in dry THF (20 mL) and cooled to 0 °C. Three min later, the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (20 mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1N, 20 mL) and DCM (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 20 mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc-DCM, 2:98) to give the oxazolidinethione *syn*-118 (270 mg, 78%, de = 99%), as white crystals. Data identical to those reported earlier.

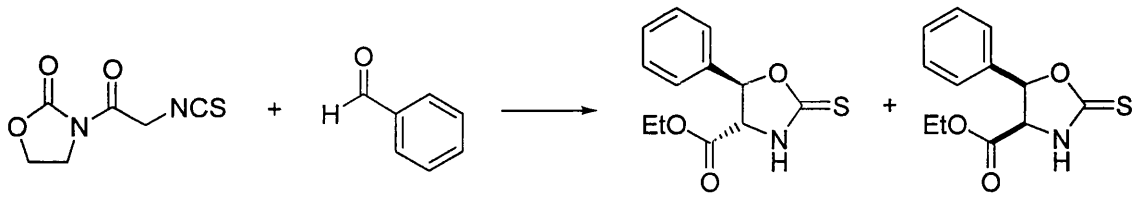
(4*R,5*R**)-5-Phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-118**



anti-144 *anti*-118

A solution of methyl magnesium bromide (3M in ether, 0.16 mL, 0.49 mmol) in ethanol (1.8 mL) at 0 °C was added by cannula transfer to a solution of the *anti*-oxazolidinethione *anti*-**144** (131 mg, 0.45 mmol, de = 99%) dissolved in dry THF (10 mL) and cooled to 0 °C. Three min later, the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (10 mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1N, 20 mL) and DCM (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 20 mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM-EtOAc, 98:2) to give the oxazolidinethione *anti*-**118** (102 mg, 91%, de = 99%), as a white solid. Data identical to those reported earlier.

III 5 Asymmetric preparation of 118; serving as a typical experimental procedure for the screening of aldehydes with 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one 116

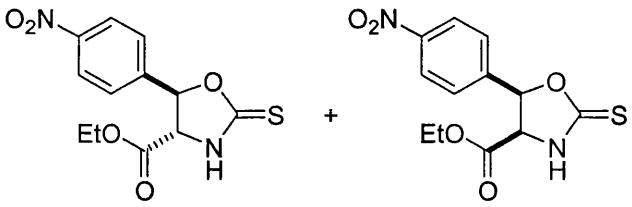


116 **12** **(4*S*,5*R*)-118** ***anti*-118**

A mixture of $Mg(ClO_4)_2$ (15 mg, 0.07 mmol), [*R*-(*R**,*R**)]-2,6-bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine **136** (28 mg, 0.08 mmol) and 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one **116** (128 mg, 0.69 mmol) was stirred for 1 h in dry DCM (15 mL) with activated powdered 4 Å MS (200 mg) under nitrogen at RT. The temperature was then lowered to -78 °C. After 15 min, benzaldehyde **12** (77 μL, 0.76 mmol) and diisopropylethylamine (24 μL, 0.14 mmol) were added and the mixture was stirred for a further 23 h at -78 °C. The reaction was quenched with sat. aqueous ammonium chloride solution (5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in dry THF (15 mL) and cooled to 0 °C. A solution of methyl magnesium bromide (3M in ether, 0.30 mL, 0.89 mmol) in ethanol (3.3 mL) at 0 °C was added to the previous solution *via* cannula transfer. Three min later, the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (5 mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1N, 10 mL) and DCM (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10

mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM-EtOAc, 98:2) to give a mixture of the (4*S*,5*R*)- and *anti*-oxazolidinethiones, **118** (114 mg, 66%, *syn*:*anti* = 75:25, $ee_{(4S,5R)}$ = 66% $[\alpha]_D^{21}$ = +19.5° (*c* = 4.2, DCM), ee_{trans} = 39% $[\alpha]_D^{21}$ = +43.7° (*c* = 1.3, DCM)), as white crystals. Data identical to those reported earlier. The enantiomers of *syn*-**118** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 8.6 min and tr_2 = 10.4 min. The enantiomers of *anti*-**118** were separated analytically using the same conditions as previously stated; tr_1 = 13.6 min and tr_2 = 39.4 min.

Ethyl 5-(4-nitrophenyl)-2-thioxo-oxazolidine-4-carboxylate 121

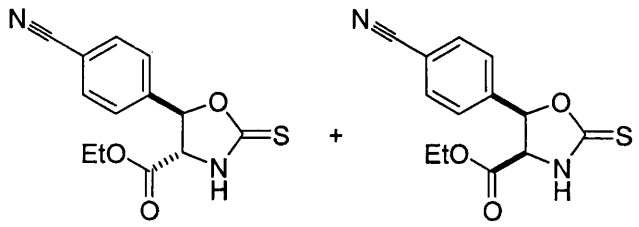


***syn*-121** ***anti*-121**

The reaction was carried out according to the typical experimental procedure III 5 with 4-nitrobenzaldehyde **37** (115 mg, 0.76 mmol). The reaction was left stirring for 20 h at -78 °C to yield both diastereomers *syn*- and *anti*-**121** (135 mg, 66%, *syn*:*anti* = 55:45, $[\alpha]_D^{21}$ = +2.4° (*c* = 3.3, DCM), $[\alpha]_D^{21}$ = +79.1° (*c* = 2.2, DCM)) as light yellow crystals. Data identical to those reported earlier. The enantiomers of *syn*-**121** could not be separated analytically by chiral HPLC using the conditions in the general information

section III 1; $tr_1 = tr_2 = 24.6$ min. Using the same conditions, the enantiomers of *anti*-**121** could not be separated neither; $tr_1 = tr_2 = 80.0$ min.

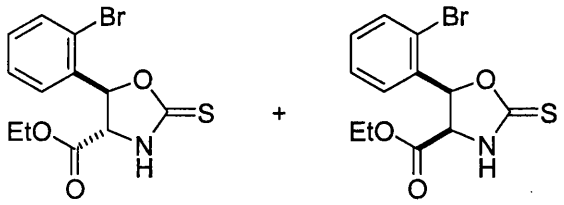
Ethyl 5-(4-cyanophenyl)-2-thioxo-oxazolidine-4-carboxylate 122



***syn*-122** ***anti*-122**

The reaction was carried out according to the typical experimental procedure III 5 with 4-cyanobenzaldehyde (100 mg, 0.76 mmol). The reaction was left stirring for 20 h at -78 °C to yield both diastereomers *syn*- and *anti*-**122** (110 mg, 58%, *syn*:*anti* = 65:35, ee_{syn} = 11% $[\alpha]_D^{21}$ = +2.3° (*c* = 3.6, DCM), ee_{trans} = 38% $[\alpha]_D^{21}$ = +36.4° (*c* = 1.4, DCM)). Data identical to those reported earlier. The enantiomers of *syn*-**122** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 20.9 min and tr_2 = 22.7 min. The enantiomers of *anti*-**122** were separated analytically using the same conditions as previously stated; tr_1 = 25.2 min and tr_2 = 74.8 min.

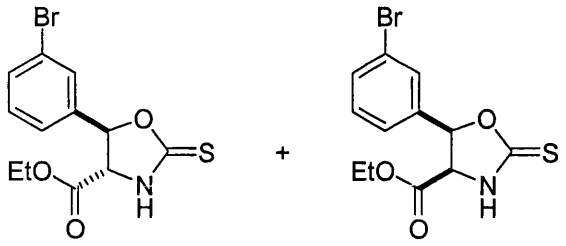
Ethyl 5-(2-bromophenyl)-2-thioxo-oxazolidine-4-carboxylate 123



***syn*-123** ***anti*-123**

The reaction was carried out according to the typical experimental procedure III 5 with 2-bromobenzaldehyde (89 μL, 0.76 mmol). The reaction was left stirring for 20 h at -78 °C to yield both diastereomers *syn*- and *anti*-**123** (89 mg, 39%, *syn*:*anti* = 50:50, ee_{syn} = 36% $[\alpha]_D^{21}$ = +16.4° (*c* = 1.7, DCM), ee_{trans} = 57% $[\alpha]_D^{21}$ = +54.6° (*c* = 1.9, DCM)). Data identical to those reported earlier. The enantiomers of *syn*-**123** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 9.0 min and tr_2 = 11.5 min. The enantiomers of *anti*-**123** were separated analytically using the same conditions as previously stated; tr_1 = 14.4 min and tr_2 = 47.8 min.

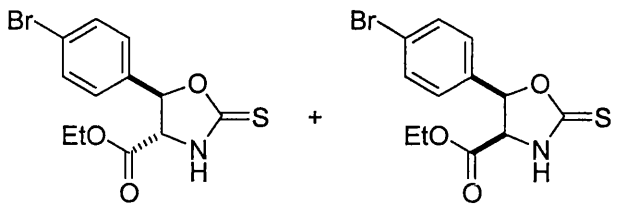
Ethyl 5-(3-bromophenyl)-2-thioxo-oxazolidine-4-carboxylate 124



***syn*-124** ***anti*-124**

The reaction was carried out according to the typical experimental procedure III 5 with 3-bromobenzaldehyde (89 μL, 0.76 mmol). The reaction was left stirring for 20 h at -78 °C to yield both diastereomers *syn*- and *anti*-**124** (91 mg, 40%, *syn*:*anti* = 45:55, ee_{syn} = 38% $[\alpha]_D^{21}$ = +10.9° (*c* = 1.9, DCM), ee_{trans} = 55% $[\alpha]_D^{21}$ = +56.3° (*c* = 2.4, DCM)). Data identical to those reported earlier. The enantiomers of *syn*-**124** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 9.1 min and tr_2 = 11.7 min. The enantiomers of *anti*-**124** were separated analytically using the same conditions as previously stated; tr_1 = 14.6 min and tr_2 = 49.3 min.

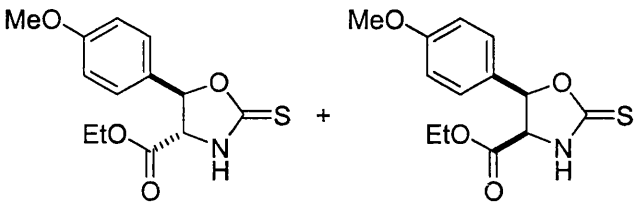
Ethyl 5-(4-bromophenyl)-2-thioxo-oxazolidine-4-carboxylate 125



***syn*-125** ***anti*-125**

The reaction was carried out according to the typical experimental procedure III 5 with 4-bromobenzaldehyde (141 mg, 0.76 mmol). The reaction was left stirring for 20 h at -78 °C to yield both diastereomers *syn*- and *anti*-**125** (165 mg, 72%, *syn*:*anti* = 70:30, ee_{syn} = 45% $[\alpha]_D^{21}$ = +10.5° (*c* = 4.8, DCM), ee_{trans} = 73% $[\alpha]_D^{21}$ = +56.4° (*c* = 1.9, DCM)). Data identical to those reported earlier. The enantiomers of *syn*-**125** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 9.5 min and tr_2 = 10.9 min. The enantiomers of *anti*-**125** were separated analytically using the same conditions as previously stated; tr_1 = 13.8 min and tr_2 = 45.9 min.

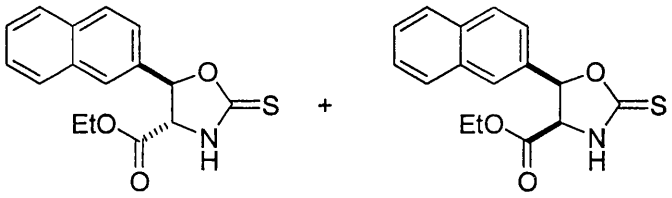
Ethyl 5-(4-methoxyphenyl)-2-thioxo-oxazolidine-4-carboxylate 127



***syn*-127** ***anti*-127**

The reaction was carried out according to the typical experimental procedure III 5 with 4-methoxybenzaldehyde (92 μL, 0.76 mmol). The reaction was left stirring for 20 h at -78 °C to yield both diastereomers *syn*- and *anti*-**127** (114 mg, 59%, *syn*:*anti* = 85:15, ee_{syn} = 77% $[\alpha]_D^{21}$ = +49.1° (*c* = 4.1, DCM), ee_{trans} = 68% $[\alpha]_D^{21}$ = +47.3° (*c* = 0.5, DCM)). Data identical to those reported earlier. The enantiomers of *syn*-**127** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 12.5 min and tr_2 = 14.2 min. The enantiomers of *anti*-**127** were separated analytically using the same conditions as previously stated; tr_1 = 16.7 min and tr_2 = 50.1 min.

Ethyl 5-(2-naphthyl)-2-thioxo-oxazolidine-4-carboxylate 128

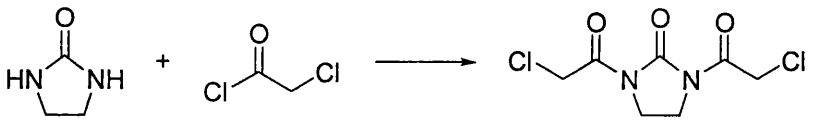


***syn*-128** ***anti*-128**

The reaction was carried out according to the typical experimental procedure III 5 with 2-naphthaldehyde (119 mg, 0.76 mmol). The reaction was left stirring for 20 h at -78 °C to yield both diastereomers *syn*- and *anti*-**128** (123 mg, 59%, *syn*:*anti* = 75:25, ee_{syn} = 77% $[\alpha]_D^{21}$ = +36.5° (*c* = 3.6, DCM), ee_{trans} = 68% $[\alpha]_D^{21}$ = +79.4° (*c* = 1.1, DCM)). Data identical to those reported earlier. The enantiomers of *syn*-**128** were separated analytically by chiral HPLC using the conditions in the general information section III 1; tr_1 = 12.4 min and tr_2 = 14.9 min. The enantiomers of *anti*-**128** were separated analytically using the same conditions as previously stated; tr_1 = 16.1 min and tr_2 = 55.8 min.

III 6 Preparation of the symmetric 1,3-bis-(2-isothiocyanato-acetyl)-imidazolidin-2-one 161

1,3-Bis-(2-chloro-acetyl)-imidazolidin-2-one 159



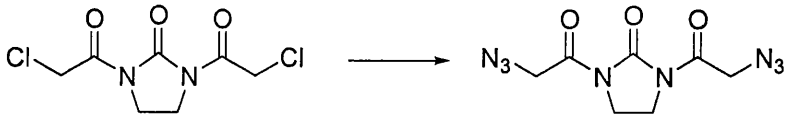
158 140 159

A solution of BuLi (2.5 M in hexane, 9.3 mL, 23.2 mmol) was added dropwise to a solution of imidazolidine-2-one **158** (1.00 g, 11.6 mmol) in dry THF (500 mL) at -78 °C and the reaction was stirred for 15 min. The temperature was allowed to reach RT overnight. Then the mixture was cooled to -78 °C for 15 min. Chloroacetyl chloride **140** (2.0 mL, 25.6 mmol) was added slowly to the reaction mixture. After 1 h, the light orange solution was warmed to RT for a further hour. The reaction was quenched with sat. aqueous ammonium chloride solution (25 mL). The mixture was concentrated under reduced pressure, taken up in water (25 mL) and extracted with DCM (3 × 25 mL). The organic portions were combined, dried ($MgSO_4$), concentrated under reduced pressure and recrystallised in DCM at RT to yield colourless prisms of *dichloroimidazolidinone* **159** (2.51 g, 90%); mp 142 °C (DCM); R_f(SiO_2, DCM) 0.14; ν_{max}(1% in KBr)/cm^{-1} 3049 (CH), 2989 (CH), 2954 (CH), 1757 (C=O), 1695 (C=O); δ_H(400 MHz; $CDCl_3$) 4.70 (4H, s, CH_2Cl), 3.96 (4H, s, CH_2CH_2); δ_C(100 MHz; $CDCl_3$) 166.6, 151.5, 44.2, 39.8; *m/z* (CI) 260 (M + NH4 + 4, 4%), 258 (M + NH_4 + 2, 18), 256 (M + NH_4, 29), 182 (M – C_2HClO + 2, 33), 180 (M – C_2HClO, 100); (Found: MNH_4^+ 256.0249.

$C_7H_{12}{}^{35}Cl_2N_3O_3$ requires *M*, 256.0250) (Found: C, 35.2; H, 3.4; N, 11.7. $C_7H_8Cl_2N_2O_3$ requires C, 35.2; H, 3.37; N, 11.7%).

1,3-Bis-(2-azido-acetyl)-imidazolidin-2-one 160

Danger, might be explosive at high temperatures!



159 **160**

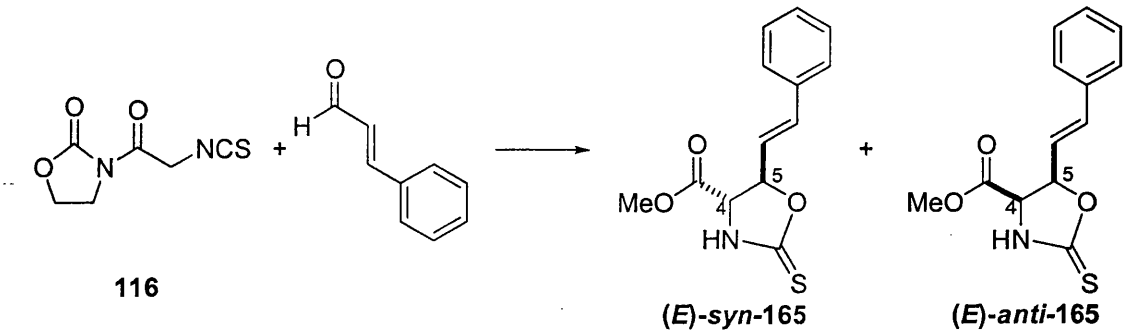
A solution of sodium azide (3.27 g, 50.3 mmol) in water (10 mL) was added to a solution of **159** (1.20 g, 5.03 mmol) in DCM (10 mL). This biphasic system was stirred and tetrabutylammonium hydrogen sulphate (0.34 g, 1.00 mmol) was added. After 1.5 h at RT, the organic layer was separated and concentrated under reduced pressure. The residue was filtered through silica (10 g) using DCM as the mobile phase. After concentration, the *diazidoimidazolidinone* **160** (0.92 g, 72%) was obtained as a colourless oil; $R_f(SiO_2$, DCM) 0.08; ν_{max}(1% in KBr)/cm^{-1} 3028 (CH), 2092 (N_3), 1753 (C=O), 1707 (C=O); δ_H(300 MHz; $CDCl_3$) 4.48 (4H, s, CH_2N_3), 3.98 (4H, s, CH_2-CH_2); δ_C(75 MHz; $CDCl_3$) 168.2, 151.7, 53.0, 39.2.

1,3-Bis-(2-isothiocyanato-acetyl)-imidazolidin-2-one 161

160 **161**

Triphenylphosphine (2.05 g, 7.83 mmol) was added to a solution of **160** (0.90 g, 3.56 mmol) in THF (20 mL) and CS_2 (20 mL) in a 1 L round bottom flask fitted with a condenser. After evolution of nitrogen, the solution gently self-refluxed and was left overnight. After concentration under reduced pressure, the residue was purified by flash chromatography (SiO_2, DCM) to yield the *diisothiocyanatoimidazolidinone* **161** (0.50 g, 49%), as a white solid which was recrystallised in DCM; mp 210 °C (DCM); R_f(SiO_2, DCM) 0.26; ν_{max}(1% in KBr)/cm^{-1} 2940 (CH), 2049 (NCS), 1757 (C=O), 1705 (C=O); δ_H(400 MHz; DMSO) 4.98 (4H, s, CH_2NCS), 3.80 (4H, s, CH_2-CH_2); δ_C(100 MHz; DMSO) 166.5, 152.1, 135.0, 50.5, 40.2; *m/z* (EI) 286 (M + 2, 11%), 284 (M^+, 100), 258 (M – C_2H_2, 11); (Found: M^+, 284.0035. $C_9H_8N_4O_3S_2$ requires *M*, 284.0032) (Found: C, 37.9; H, 2.8; N, 19.7. $C_9H_8N_4O_3S_2$ requires C, 38.0; H, 2.84; N, 19.7%).

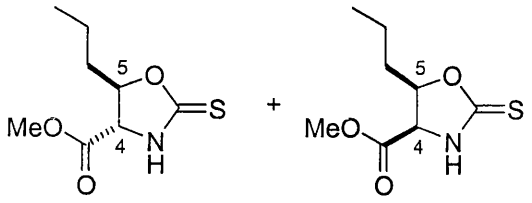
III 7 Preparation of (4*S**,5*R**)-5-(*E*)-styryl-2-thioxo-oxazolidine-4-carboxylic acid methyl ester *syn*-165 and (4*R**,5*R**)-5-(*E*)-styryl-2-thioxo-oxazolidine-4-carboxylic acid methyl ester *anti*-165; serving as a typical experimental procedure for the screening of several electrophiles



A mixture of $Mg(ClO_4)_2$ (36 mg, 0.16 mmol) and 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one **116** (300 mg, 1.61 mmol) was stirred for 15 min in dry THF (7 mL) under nitrogen at RT. The temperature was then lowered to -78 °C. After 15 min, *E*-cinnamaldehyde (223 μL, 1.77 mmol) and triethylamine (45 μL, 0.32 mmol) were added and the mixture was stirred for a further 2 h at -78 °C. The reaction was quenched with sat. aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in dry THF (35 mL) and cooled to 0 °C. A solution of methyl magnesium bromide (3M in ether, 0.70 mL, 2.10 mmol) in methanol (10 mL) at 0 °C was added to the previous solution by cannula transfer. Three min later, the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (10 mL). The mixture was concentrated under reduced pressure, taken up in aqueous

HCl (1N, 20 mL) and DCM (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 20 mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc-DCM, 2:98) to give in order of elution the *syn-oxazolidinethione syn*-**165** (77 mg, 18%), as yellow crystals: mp 137 °C (DCM-hexane); R_f(SiO_2, DCM-EtOAc, 98:2) 0.30; ν_{max}(1% in KBr)/cm^{-1} 3275 (NH), 2958 (CH), 1765 (C=O), 1676 (Ar), 1654 (Ar), 1522 (NHC=S), 1173 (CO); δ_H(300 MHz; $CDCl_3$) 7.64 (1H, s, NH), 7.44-7.30 (5H, m, C_6H_5), 6.84 (1H, d, *J* 15.8, C*H*-C_6H_5), 6.29 (1H, dd, *J* 15.8, 7.4, C*H*=CH-C6H5), 5.61-5.56 (1H, m, 5-H), 4.43 (1H, d, *J* 6.2, 4-H), 3.87 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 189.3, 168.7, 136.5, 135.2, 129.5, 129.2, 127.5, 123.0, 85.9, 62.9, 53.9; *m/z* (EI) 263 (M^+, 100%); (Found: MH^+, 264.0691. $C_{13}H_{14}NO_3S$ requires *M*, 264.0689) (Found: C, 59.3; H, 5.1; N, 5.4. $C_{13}H_{13}NO_3S$ requires C, 59.3; H, 4.98; N, 5.3%); and the *anti*-oxazolidinethione *anti*-**165** (32 mg, 8%) as a yellow oil. *Anti*-**165** decomposed quickly after the column chromatography and was not fully characterised: R_f(SiO_2, DCM-EtOAc, 98:2) 0.13; δ_H(300 MHz; $CDCl_3$) 7.47-7.32 (5H, m, C_6H_5), 6.80 (1H, d, *J* 15.6, C*H*C_6H_5), 6.09 (1H, dd, *J* 15.6, 7.8, C*H*=C*H*C_6H_5), 5.68-5.62 (1H, m, 5-H), 4.76 (1H, d, *J* 9.3, 4-H), 3.70 (3H, s, CH_3).

Preparation of (4*S,5*R**)-5-propyl-2-thioxo-oxazolidine-4-carboxylic acid methyl ester *syn*-166 and (4*R**,5*R**)-5-propyl-2-thioxo-oxazolidine-4-carboxylic acid methyl ester *anti*-166**

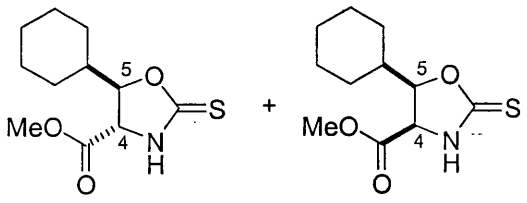


***syn*-166** ***anti*-166**

The reaction was carried out according to the typical experimental procedure III 7 with butyraldehyde (158 μL, 1.77 mmol). The reaction was left stirring for 2 h at -78 °C and gave in order of elution the *syn-oxazolidinethione syni*-**166** (65 mg, 20%) as a white crystal: mp 72 °C (DCM); R_f(SiO_2, DCM-EtOAc, 98:2) 0.19; ν_{max}(1% in KBr)/cm^{-1} 3334 (NH), 2952 (CH), 1733 (C=O), 1515 (NHC=S), 1199 (CO); δ_H(300 MHz; $CDCl_3$) 7.64 (1H, s, NH), 4.97 (1H, dt, *J* 7.2, 6.0, 5-H), 4.23 (1H, d, *J* 6.0, 4-H), 3.84 (3H, s, O-CH_3), 1.97-1.76 (2H, m, CH_2), 1.67-1.44 (2H, m, CH_2), 1.00 (3H, t, *J* 7.3, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 189.6, 169.1, 85.8, 62.3, 53.8, 37.3, 18.2, 14.0; *m/z* (CI) 204 (M + H, 100%), 172 (M – CH_3O, 94); (Found: MH^+, 204.0691. $C_8H_{14}NO_3S$ requires *M*, 204.0689); and the *anti-oxazolidinethione anti*-**166** (70 mg, 21%) as a colourless oil: R_f(SiO_2, DCM-EtOAc, 98:2) 0.12; ν_{max}($CHCl_3$, 0.05 M)/cm^{-1} 3443 (NH), 2966 (CH), 2877 (CH), 1753 (C=O), 1485 (NHC=S); δ_H(300 MHz; $CDCl_3$) 8.13 (1H, s, NH), 5.08-5.01 (1H, m, 5-H), 4.64 (1H, d, *J* 9.2, 4-H), 3.80 (3H, s, OCH_3), 1.67-1.40 (4H, m, C_2H_4), 0.94 (3H, t, *J* 6.9, CH_3CH_2); δ_C(75 MHz; $CDCl_3$) 190.4, 168.8, 84.8, 61.4, 53.4, 32.5, 19.2, 14.0; *m/z* (CI) 221 (M + NH_4, 46%), 204 (M + H, 100), 189 (M – CH_2, 12),

172 (M – CH_3O, 89); (Found: MH^+, 204.0688. $C_8H_{14}NO_3S$ requires *M*, 204.0689) (Found: C, 47.2; H, 6.5; N, 6.9. $C_8H_{13}NO_3S$ requires C, 47.3; H, 6.45; N, 6.9%).

Preparation of (4*S,5*R**)-5-cyclohexyl-2-thioxo-oxazolidine-4-carboxylic acid methyl ester *syn*-167 and (4*R**,5*R**)-5-cyclohexyl-2-thioxo-oxazolidine-4-carboxylic acid methyl ester *anti*-167**

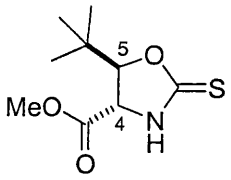


***syn*-167** ***anti*-167**

The reaction was carried out according to the typical experimental procedure III 7 with cyclo-hexylcarboxaldehyde **20** (214 μL, 1.77 mmol). The reaction was left stirring for 3 h at -78 °C and gave in order of elution the *syn-oxazolidinethione syn*-**167** (69 mg, 20%) as white crystals: mp 86 °C (DCM); R_f(SiO_2, DCM-EtOAc, 98:2) 0.17; ν_{max}(1% in KBr)/cm^{-1} 3365 (NH), 2931 (CH), 2856 (CH), 1739 (C=O), 1505 (NHC=S), 1195 (CO); δ_H(300 MHz; $CDCl_3$) 8.09 (1H, s, NH), 4.76 (1H, t, *J* 5.6, 5-H), 4.32 (1H, d, *J* 5.6, 4-H), 3.80 (3H, s, CH_3), 1.88-1.68 (6H, m, C_6H_{11}), 1.27-1.06 (5H, m, C_6H_{11}); δ_C(75 MHz; $CDCl_3$) 189.6, 169.7, 89.8, 59.9, 53.8, 42.3, 27.9, 27.4, 26.4, 25.9, 25.7; *m/z* (CI) 244 (M + H, 100%), 212 (M – CH_3O, 51); (Found: MH^+, 244.0998. $C_{11}H_{18}NO_3S$ requires *M*, 244.1002) (Found: C, 54.1; H, 7.1; N, 5.8. $C_{11}H_{17}NO_3S$ requires C, 54.3; H, 7.04; N, 5.8%); and the *anti-oxazolidinethione anti*-**167** (74 mg, 21%) as white crystals: mp 130 °C (DCM); R_f(SiO_2, DCM-EtOAc, 98:2) 0.12; ν_{max}(1% in KBr)/cm^{-1} 3175 (NH), 2941 (CH), 2853 (CH), 1739 (C=O), 1518 (NHC=S), 1178 (CO); δ_H(300 MHz;

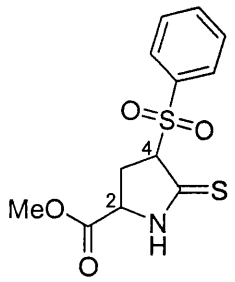
$CDCl_3$) 7.32 (1H, s, NH), 4.67 (1H, t, *J* 8.3, 5-H), 4.51 (1H, d, *J* 8.3, 4-H), 3.76 (3H, s, CH_3), 1.87-1.58 (6H, m, C_6H_{11}) 1.18-1.05 (5H, m, C_6H_{11}); δ_C(75 MHz; $CDCl_3$) 190.9, 168.7, 89.4, 60.9, 53.4, 39.0, 29.7, 28.3, 26.2, 25.9, 25.6; *m/z* (CI) 244 (M + H, 100%), 212 (M – CH_3O, 26); (Found: M^+, 244.0999. $C_{11}H_{18}NO_3S$ requires *M*, 244.1002) (Found: C, 54.5; H, 7.0; N, 6.0. $C_{11}H_{17}NO_3S$ requires C, 54.3; H, 7.04; N, 5.8%).

Preparation of (4*S,5*R**)-5-*tert*-Butyl-2-thioxo-oxazolidine-4-carboxylic acid methyl ester *syn*-168**



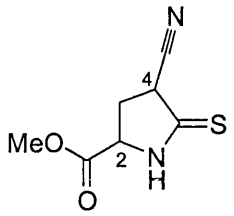
The reaction was carried out according to the typical experimental procedure III 7 with pivaldehyde **46** (192 μL, 1.77 mmol). The reaction was left stirring for 3 h at -78 °C and gave the *syn-oxazolidinethione syn*-**168** (15 mg, 4%) as light yellow crystals: mp 72 °C (DCM-hexane); R_f(SiO_2, DCM-EtOAc, 98:2) 0.19; ν_{max}(1% in KBr)/cm^{-1} 3357 (NH), 3270 (CH), 2964 (CH), 1727 (C=O), 1505 (NHC=S), 1171 (CO); δ_H(300 MHz; $CDCl_3$) 7.83 (1H, s, NH), 4.69 (1H, d, *J* 5.3, 5-H), 4.29 (1H, d, *J* 5.3, 4-H), 3.82 (3H, s, O-CH_3), 1.01 (9H, s, $C(CH_3)_3$); δ_C(75 MHz; $CDCl_3$) 189.6, 169.8, 93.3, 58.4, 53.8, 35.3, 24.7; *m/z* (CI) 218 (M + H, 71%), 186 (M – CH_3O, 100); (Found: MH^+, 218.0841. $C_9H_{16}NO_3S$ requires *M*, 218.0845).

Methyl 4-benzenesulfonyl-5-thioxopyrrolidine-2-carboxylate 169



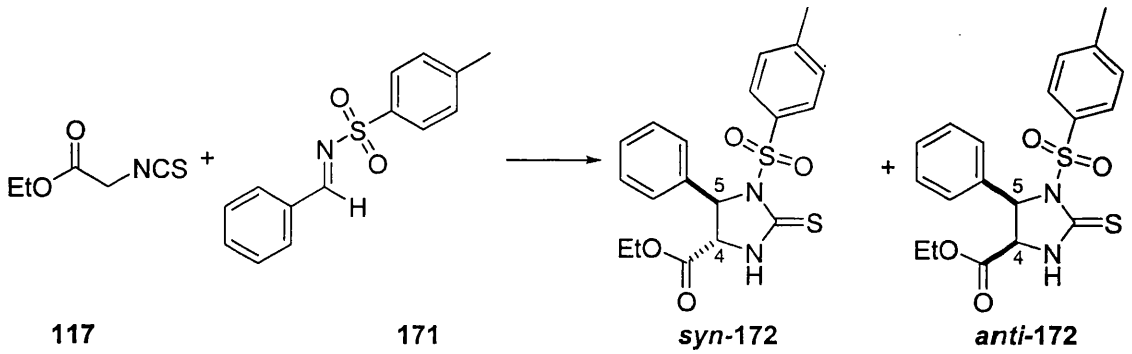
The reaction was carried out according to the typical experimental procedure III 7 with phenyl vinyl sulfone (298 mg, 1.77 mmol). The reaction was left stirring during 4 h at RT and gave a mixture of *syn*- and *anti*-**169** (9 mg, 2%, *syn*:*anti* = 50:50) as a colourless solid that was not fully characterised: R_f(SiO_2, DCM-EtOAc, 98:2) 0.20 and 0.10; ν_{max}(1% in KBr)/cm^{-1} 3305 (NH), 2925 (CH), 1740 (C=O), 1584 (Ar), 1512 (NHC=S), 1377 (SO_2), 1143 (CO); δ_H(300 MHz; $CDCl_3$) 8.04 (1H, s, NH), 7.97 (1H, s, NH), 7.94-7.91 (4H, m, C_6H_5), 7.74-7.67 (2H, m, C_6H_5), 7.60-7.54 (4H, m, C_6H_5), 4.81 (1H, dd, *J* 9.2, 7.5, 4-H), 4.50 (1H, d, *J* 9.8, 4-H), 4.32 (1H, dd, *J* 9.2, 1.6, 2-H), 4.31 (1H, dd, *J* 9.8, 2.6, 2-H), 3.85 (3H, s, CH_3), 3.83 (3H, s, CH_3), 3.48-3.38 (2H, m, CH_AH_B), 3.00 (1H, dt, *J* 15.3, 9.8, CH_AH_B), 2.74 (1H, dt, *J* 14.7, 9.2, CH_AH_B); *m/z* (CI) 317 (M + NH_4, 100%), 300 (M + H, 71); (Found: MH^+, 300.0359. $C_{12}H_{14}NO_4S_2$ requires *M*, 300.0359).

Methyl 4-cyano-5-thioxopyrrolidine-2-carboxylate 170



The reaction was carried out according to the typical experimental procedure III 7 with acrylonitrile (123 μL, 1.77 mmol). The reaction was left stirring during 4 h at RT and gave *syn*- or *anti*-**170** (15 mg, 5%) as a light yellow solid: mp 104 °C (DCM); R_f(SiO_2, DCM-EtOAc, 98:2) 0.14; ν_{max}(1% in KBr)/cm^{-1} 3163 (NH), 3014 (CH), 2883 (CH), 2257 (CN), 1746 (C=O), 1538 (NHC=S), 1190 (CO); δ_H(300 MHz; $CDCl_3$) 8.52 (1H, s, NH), 4.62 (1H, t, *J* 8.0, 4-H), 4.04 (1H, t, *J* 9.0, 2-H), 3.84 (3H, s, CH_3), 3.04 (1H, ddd, *J* 8.0, 9.0, 13.2, CH_AH_B), 2.66 (1H, ddd, *J* 8.0, 9.0, 13.2, CH_AH_B); *m/z* (CI) 202 (M + NH_4, 100%), 185 (M + H, 13); (Found: MNH_4^+, 202.0648. $C_7H_{12}N_3O_2S$ requires *M*, 202.0645).

III 8 Preparation of (4*S**,5*R**)-5-phenyl-2-thioxo-1-(toluene-4-sulphonyl)-imidazolidine-4-carboxylic acid ethyl ester *syn*-172 and (4*R**,5*R**)-5-phenyl-2-thioxo-1-(toluene-4-sulphonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-172; serving as a typical experimental procedure for the screening of catalysts and imines with ethyl isothiocyanatoacetate 117

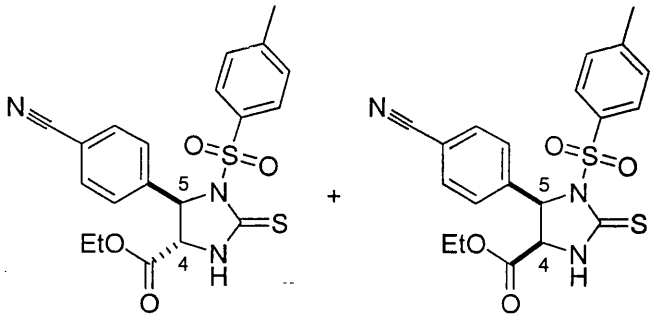


117 **171** ***syn*-172** ***anti*-172**

A mixture of $Mg(OTf)_2$ (44 mg, 0.14 mmol), bipyridine (22 mg, 0.14 mmol) and *N*-(4-toluenesulphonyl)benzaldimine **171** (716 mg, 2.76 mmol) was stirred for 10 min in dry THF (5.5 mL) under nitrogen at RT. Ethyl isothiocyanatoacetate **117** (170 μL, 1.38 mmol) and triethylamine (39 μL, 0.28 mmol) were then added and the mixture was stirred for a further 18 hours. The reaction was quenched with sat. aqueous ammonium chloride solution (5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM-EtOAc, 98:2) to give in order of elution the *syn-imidazolidinethione syn*-**172** (247 mg, 44%), as viscous oil, which recrystallised from DCM/hexane: mp 168 °C (DCM-hexane); R_f(SiO_2, DCM-EtOAc, 98:2) 0.43;

ν_{max}(1% in KBr)/cm^{-1} 3337 (NH), 2957 (CH), 1744 (C=O), 1594 (Ar), 1490 (NHC=S), 1349 (SO_2), 1164 (SO_2); δ_H(400 MHz; $CDCl_3$) 7.49 (2H, d, *J* 8.2, C_6H_4), 7.38-7.31 (5H, m, C_6H_5), 7.20 (1H, s, NH), 7.09 (2H, d, *J* 8.2, C_6H_4), 5.92 (1H, d, *J* 2.2, 5-H), 4.32-4.23 (2H, m, CH_2), 4.16 (1H, d, *J* 2.2, 4-H), 2.36 (3H, s, $CH_3C_6H_4$), 1.32 (3H, t, *J* 7.2, CH_3CH_2); δ_C(100 MHz; $CDCl_3$) 179.6, 168.4, 145.1, 138.8, 134.9, 129.6, 129.4, 129.0, 126.8, 67.8, 63.5, 63.3, 22.1, 14.6; *m/z* (CI) 422 (M + NH_4, 57%), 405 (M + H, 100%); (Found: MH^+, 405.0936. $C_{19}H_{21}N_2O_4S_2$ requires *M*, 405.0937) (Found: C, 56.4; H, 4.9; N, 6.9. $C_{19}H_{20}N_2O_4S_2$ requires C, 56.4; H, 4.98; N, 6.9%); and the *anti-imidazolidinethione anti*-**172** (127 mg, 23%), as viscous oil that recrystallised from chloroform: mp 201 °C ($CHCl_3$); R_f(SiO_2, DCM-EtOAc, 98:2) 0.26; ν_{max}(1% in KBr)/cm^{-1} 3176 (NH), 3011 (CH), 2985 (CH), 2933 (CH), 1741 (C=O), 1594 (Ar), 1524 (NHC=S), 1369 (SO_2), 1172 (SO_2); δ_H(300 MHz; DMSO) 10.02 (1H, s, NH), 7.56 (2H, d, *J* 8.3, C_6H_4), 7.41-7.31 (3H, m, C_6H_5), 7.27 (2H, d, *J* 8.3, C_6H_4), 7.19-7.16 (2H, m, C_6H_5), 6.04 (1H, d, *J* 10.2, 5-H), 5.19 (1H, d, *J* 10.2, 4-H), 3.67 (1H, dq, *J* 10.8, 7.1, CH_AH_B), 3.55 (1H, dq, *J* 10.8, 7.1, CH_AH_B), 2.36 (3H, s, $CH_3C_6H_4$), 0.73 (3H, t, *J* 7.1, CH_3CH_2); δ_C(75 MHz; DMSO) 179.1, 167.0, 144.9, 136.4, 135.7, 129.6, 129.2, 128.6, 127.8, 125.9, 66.0, 61.29, 61.27, 21.4, 13.6; *m/z* (CI) 405 (M + H, 25%), 251 (M - $SO_2C_6H_4CH_3$ + 2, 100), 91 ($C_6H_4CH_3$, 15); (Found: MH^+, 405.0934. $C_{19}H_{21}N_2O_4S_2$ requires *M*, 405.0937).

Preparation of (4*S,5*R**)-5-(4-cyanophenyl)-2-thioxo-1-(toluene-4-sulphonyl)-imidazolidine-4-carboxylic acid ethyl ester *syn*-173 and (4*R**,5*R**)-5-(4-cyanophenyl)-2-thioxo-1-(toluene-4-sulphonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-173**

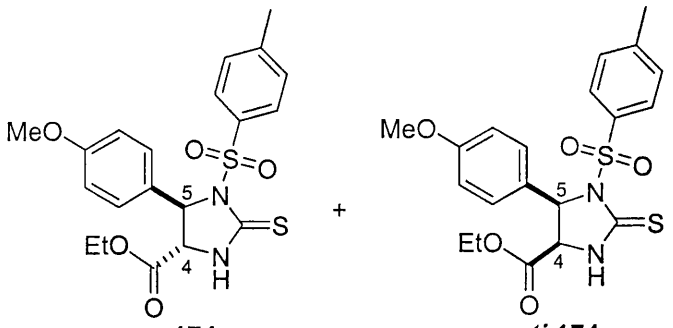


syn-173 *anti*-173

The reaction was carried out according to the typical experimental procedure III 8 with *N*-(4-toluenesulphonyl)-4-cyanobenzaldimine (569 mg, 2.00 mmol). The reaction was left stirring for 18 h at RT and gave in order of elution the *syn-imidazolidinethione syn*-**173** (195 mg, 45%), as colourless crystals that quickly decomposed preventing mass spectrometry analysis and furnished a low carbon percentage for the elemental analysis: mp 180 °C (DCM-hexane); R_f(SiO_2, DCM-EtOAc, 98:2) 0.18; ν_{max}(1% in KBr)/cm^{-1} 3147 (NH), 2998 (CH), 2229 (Ar-CN), 1755 (C=O), 1596 (Ar), 1521 (NHC=S), 1362 (SO_2), 1168 (SO_2), 1136 (CO); δ_H(300 MHz; $CDCl_3$) 7.71-7.64 (4H, m, C_6H_4CN), 7.52-7.49 (2H, m, C_6H_4Me), 7.22 (2H, d, *J* 8.1, C_6H_4Me), 7.10 (1H, s, NH), 6.00 (1H, d, *J* 2.8, 5-H), 4.38-4.22 (2H, m, CH_2), 4.10 (1H, d, *J* 2.8, 4-H), 2.42 (3H, s, $CH_3C_6H_4$), 1.32 (3H, t, *J* 7.1, CH_3CH_2); δ_C(75 MHz; $CDCl_3$) 179.3, 167.8, 145.7, 143.8, 134.4, 133.1, 129.3, 129.1, 127.2, 118.1, 113.2, 66.8, 63.3, 62.8, 21.7, 14.1; (Found: C, 55.5; H, 4.5; N, 9.6. $C_{20}H_{19}N_3O_4S_2$ requires C, 55.9; H, 4.46; N, 9.8%); and the *anti-imidazolidinethione anti*-**173** (136 mg, 32%) as white crystals: mp 172 °C (DCM-

hexane); R_f(SiO_2, DCM-EtOAc, 98:2) 0.13; ν_{max}(1% in KBr)/cm^{-1} 3340 (NH), 2229 (Ar-CN), 1748 (C=O), 1499 (NHC=S), 1338 (SO_2), 1168 (SO_2); δ_H(400 MHz; DMSO) 10.08 (1H, s, NH), 7.86 (2H, d, *J* 8.6, C_6H_4), 7.68 (2H, d, *J* 8.6, C_6H_4), 7.38 (2H, d, *J* 8.6, C_6H_4), 7.32 (2H, d, *J* 8.6, C_6H_4), 6.20 (1H, d, *J* 10.5, 5-H), 5.18 (1H, d, *J* 10.5, 4-H), 3.69 (1H, dq, *J* 10.8, 7.1, CH_AH_B), 3.55 (1H, dq, *J* 10.8, 7.1, CH_AH_B), 2.38 (3H, s, $CH_3C_6H_4$), 0.77 (3H, t, *J* 7.1, CH_3CH_2); δ_C(100 MHz; DMSO) 179.3, 167.1, 145.5, 142.3, 135.6, 133.0, 129.7, 129.5, 129.0, 119.1, 112.2, 65.7, 62.0, 61.6, 22.0, 14.2; *m/z* (CI) 447 (M + NH_4, 14%), 430 (M + H, 100); (Found: MH^+, 430.0895. $C_{20}H_{20}N_3O_4S_2$ requires *M*, 430.0890).

Preparation of (4*S,5*R**)-5-(4-methoxyphenyl)-2-thioxo-1-(toluene-4-sulphonyl)-imidazolidine-4-carboxylic acid ethyl ester *syn*-174 and (4*R**,5*R**)-5-(4-methoxyphenyl)-2-thioxo-1-(toluene-4-sulphonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-174**

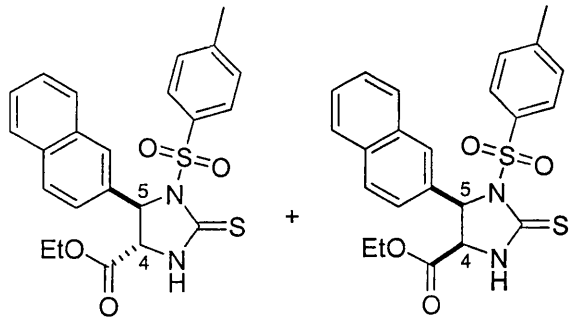


syn-174 *anti*-174

The reaction was carried out according to the typical experimental procedure III 8 with *N*-(4-toluenesulphonyl)-4-methoxybenzaldimine (799 mg, 2.76 mmol). The reaction was left stirring for 28 h at RT and gave in order of elution the *syn-imidazolidinethione* ***syn*-174** (191 mg, 32%), as white crystals: mp 126 °C (DCM-hexane); R_f(SiO_2, DCM-

EtOAc, 98:2) 0.26; ν_{max}(1% in KBr)/cm^{-1} 3334 (NH), 2979 (CH), 1751 (C=O), 1600 (Ar), 1483 (NHC=S), 1358 (SO_2), 1222 (CO), 1168 (SO_2), 1061 (CO); δ_H(400 MHz; $CDCl_3$) 7.49-7.47 (2H, m, Ar), 7.39 (1H, app. s, NH), 7.25-7.23 (2H, m, Ar), 7.10-7.08 (2H, m, Ar), 6.86-6.84 (2H, m, Ar), 5.86 (1H, d, *J* 2.3, 5-H), 4.31-4.22 (2H, m, CH_2), 4.16-4.15 (1H, m, 4-H), 3.82 (3H, s, OCH_3), 2.35 (3H, s, $CH_3C_6H_4$), 1.31 (3H, t, *J* 7.0, CH_3CH_2); δ_C(100 MHz; $CDCl_3$) 179.5, 168.5, 160.3, 145.0, 135.1, 131.0, 129.6, 129.0, 128.3, 114.7, 67.5, 63.6, 63.2, 55.8, 22.1, 14.6; *m/z* (CI) 452 (M + NH_4, 29%), 435 (M + H, 100); (Found: MH^+, 435.1046. $C_{20}H_{23}N_2O_5S_2$ requires *M*, 435.1043) (Found: C, 55.4; H, 5.1; N, 6.5. $C_{20}H_{22}N_2O_5S_2$ requires C, 55.3; H, 5.10; N, 6.5%); and the *anti-imidazolidinethione anti*-**174** (71 mg, 12%). *Anti*-**174** was obtained as a mixture with tosylamine and could not be further purified, no mass spectrometry or elemental analysis experiment was attempted: R_f(SiO_2, DCM-EtOAc, 98:2) 0.15; δ_H(300 MHz; $CDCl_3$) 7.37 (2H, d, *J* 7.7, Ar), 7.11 (2H, d, *J* 8.9, Ar), 7.01 (2H, d, *J* 8.9, Ar), 6.86 (1H, s, NH), 6.77 (2H, d, *J* 7.7, Ar), 5.92 (1H, d, *J* 8.9, 5-H), 4.96 (1H, d, *J* 8.9, 4-H), 3.87-3.73 (2H, m, CH_2), 3.79 (3H, s, OCH_3), 2.34 (3H, s, $CH_3C_6H_4$), 0.85 (3H, t, *J* 7.7, CH_3CH_2); δ_C(75 MHz; $CDCl_3$) 179.4, 166.1, 160.4, 144.8, 134.7, 129.6, 129.5, 128.6, 126.5, 113.8, 66.3, 62.0, 60.8, 55.4, 21.6, 13.6.

Preparation of (4*S,5*R**)-5-(2-naphthyl)-2-thioxo-1-(toluene-4-sulphonyl)-imidazolidine-4-carboxylic acid ethyl ester *syn*-175 and (4*R**,5*R**)-5-(2-naphthyl)-2-thioxo-1-(toluene-4-sulphonyl)-imidazolidine-4-carboxylic acid ethyl ester *anti*-175**



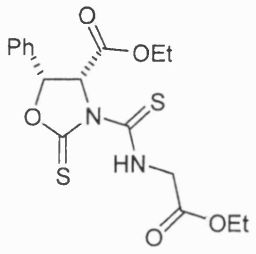
***syn*-175** ***anti*-175**

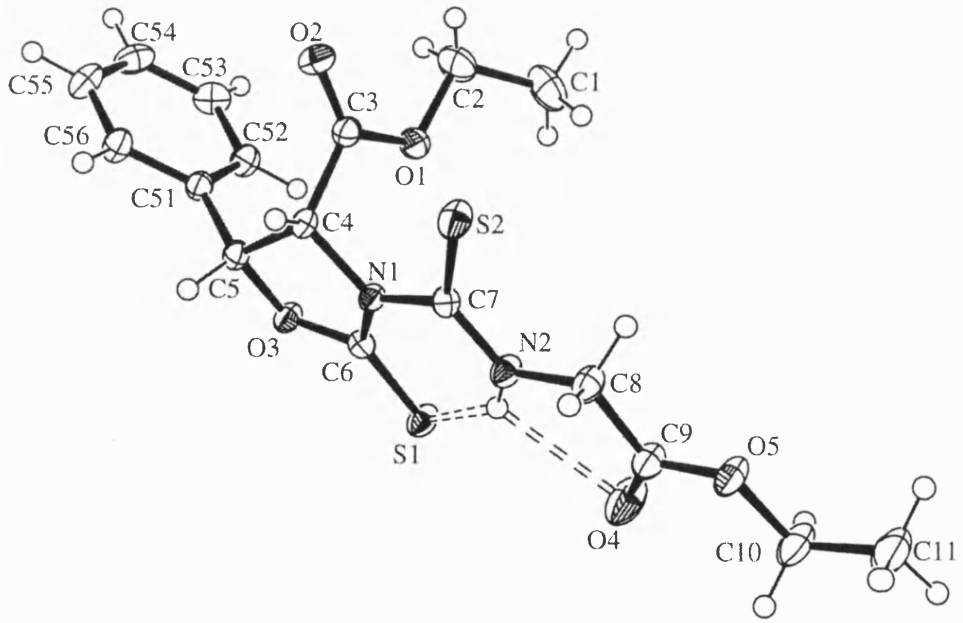
The reaction was carried out according to the typical experimental procedure III 8 with *N*-(4-toluenesulphonyl)-2-naphthaldimine (619 mg, 2.00 mmol. The reaction was left stirring for 17 h at RT and gave in order of elution the *syn-imidazolidinethione syn*-**175** (181 mg, 40%), as white crystals: mp 212 °C (DCM-hexane); R_f(SiO_2, DCM-EtOAc, 98:2) 0.42; ν_{max}(1% in KBr)/cm^{-1} 3332 (NH), 3000 (CH), 1742 (C=O), 1599 (Ar), 1563 (Ar), 1485 (NHC=S), 1370 (SO_2), 1168 (SO_2); δ_H(400 MHz; $CDCl_3$) 7.84-7.77 (4H, m, Ar), 7.54-7.47 (4H, m, Ar), 7.34-7.32 (1H, m, Ar), 7.14 (1H, app. s, NH), 6.98-6.95 (2H, m, Ar), 6.1 (1H, d, *J* 2.7, 5-H), 4.35-4.26 (2H, m, CH_2), 4.22 (1H, dd, *J* 2.7, 1.2, 4-H), 2.30 (3H, s, $CH_3C_6H_4$), 1.34 (3H, t, *J* 7.2, CH_3CH_2); δ_C(100 MHz; $CDCl_3$) 179.8, 168.4, 145.1, 135.8, 134.9, 133.6, 133.2, 129.6, 129.5, 128.9, 128.5, 127.9, 127.1, 127.0, 126.6, 123.5, 68.1, 63.5, 63.3, 22.0, 14.6; *m/z* (CI) 472 (M + NH_4, 21%), 455 (M + H, 100); (Found: MH^+, 455.1092. $C_{23}H_{22}N_2O_4S_2$ requires *M*, 455.1094); and the *anti-imidazolidinethione anti*-**175** (160 mg, 35%) as white crystals: mp 88 °C (DCM-hexane); R_f(SiO_2, DCM-EtOAc, 98:2) 0.24; ν_{max}(1% in KBr)/cm^{-1} 3309 (NH), 2961

(CH), 1746 (C=O), 1612 (Ar), 1593 (Ar), 1514 (Ar), 1488 (NHC=S), 1352 (SO_2), 1161 (SO_2); δ_H(400 MHz; DMSO) 10.06 (1H, s, NH), 7.93-7.85 (3H, m, Ar), 7.60-7.51 (4H, m, Ar), 7.26-7.17 (4H, m, Ar), 6.23 (1H, d, *J* 10.1, 5-H), 5.24 (1H, d, *J* 10.1, 4-H), 3.56 (1H, dq, *J* 10.8, 7.1, CH_AH_B), 3.41 (1H, dq, *J* 10.8, 7.1, CH_AH_B), 2.32 (3H, s, $CH_3C_6H_4$), 0.54 (3H, t, *J* 7.1, CH_3CH_2); δ_C(100 MHz; DMSO) 179.4, 167.2, 145.2, 135.9, 134.2, 133.5, 132.9, 129.5, 129.4, 128.5, 128.2, 127.6, 127.4, 127.3, 125.3, 66.7, 61.8, 61.7, 21.9, 14.1; *m/z* (CI) 472 (M + NH_4, 6%), 455 (M + H, 100); (Found: MH^+, 455.1093. $C_{23}H_{22}N_2O_4S_2$ requires *M*, 455.1094).

Appendix A

(4*R**,5*R**)-3-Ethoxycarbonylmethylthiocarbamoyl-5-phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester *anti*-119





Appendix A

Table 1. Crystal data and structure refinement for ***anti*-119**.

Identification code	k03mcw
Empirical formula	C17 H20 N2 O5 S2
Formula weight	396.47
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system	monoclinic
Space group	C 2/c
Unit cell dimensions	a = 22.9100(3) A alpha = 90 deg.
	b = 7.19300(10) A beta = 95.3(10) deg.
	c = 22.7610(3) A gamma = 90 deg.
Volume	3734.94(9) A^3
Z, Calculated density	8, 1.410 Mg/m^3
Absorption coefficient	0.316 mm^-1
F(000)	1664
Crystal size	0.60 x 0.30 x 0.25 mm
Colour, shape	colourless block
Theta range for data collection	3.57 to 30.05 deg.
Limiting indices	-32<=h<=32, -10<=k<=10, -31<=l<=32
Reflections collected / unique	28652 / 5441 [R(int) = 0.0597]
Completeness to theta = 30.05	99.6 %
Max. and min. transmission	0.9253 and 0.8332
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5441 / 0 / 315
Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma(I)]	R1 = 0.0344, wR2 = 0.0825
R indices (all data)	R1 = 0.0483, wR2 = 0.0892
Largest diff. peak and hole	0.347 and -0.359 e.A^-3

Appendix A

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for ***anti*-119**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	3461(1)	2675(1)	3405(1)	24(1)
S(2)	3961(1)	8049(1)	2162(1)	27(1)
C(1)	4878(1)	2318(3)	1634(1)	42(1)
C(2)	4334(1)	2803(3)	1259(1)	39(1)
C(3)	3496(1)	4616(2)	1415(1)	21(1)
C(4)	3072(1)	5129(2)	1866(1)	18(1)
C(5)	2582(1)	3668(2)	1905(1)	19(1)
C(51)	2467(1)	2377(2)	1387(1)	20(1)
C(52)	2795(1)	768(2)	1340(1)	24(1)
C(53)	2691(1)	-375(2)	848(1)	28(1)
C(54)	2263(1)	91(2)	403(1)	31(1)
C(55)	1935(1)	1694(2)	449(1)	31(1)
C(56)	2034(1)	2831(2)	941(1)	25(1)
C(6)	3208(1)	3518(2)	2762(1)	18(1)
C(7)	3786(1)	6449(2)	2645(1)	18(1)
C(8)	4473(1)	7669(2)	3423(1)	25(1)
C(9)	4714(1)	7038(2)	4027(1)	26(1)
C(10)	5429(1)	7589(2)	4823(1)	36(1)
C(11)	5908(1)	8942(3)	4993(1)	41(1)
N(1)	3353(1)	5109(1)	2473(1)	17(1)
N(2)	4028(1)	6359(2)	3195(1)	22(1)
O(1)	3908(1)	3457(1)	1649(1)	25(1)
O(2)	3440(1)	5143(1)	912(1)	29(1)
O(3)	2788(1)	2602(1)	2431(1)	21(1)
O(4)	4546(1)	5685(2)	4270(1)	43(1)
O(5)	5141(1)	8163(1)	4251(1)	29(1)

Table 3. Bond lengths [Å] for ***anti*-119**.

S(1)-C(6)	1.6396(12)
S(1)-H	2.277(19)
S(2)-C(7)	1.6659(12)
C(1)-C(2)	1.486(2)
C(1)-H(1A)	1.00(2)
C(1)-H(1B)	0.95(2)
C(1)-H(1C)	0.97(2)
C(2)-O(1)	1.4572(16)
C(2)-H(2A)	0.96(2)
C(2)-H(2B)	0.96(2)
C(3)-O(2)	1.2021(14)
C(3)-O(1)	1.3336(15)
C(3)-C(4)	1.5232(16)
C(4)-N(1)	1.4695(14)
C(4)-C(5)	1.5463(16)
C(4)-H(4)	0.950(16)
C(5)-O(3)	1.4636(14)
C(5)-C(51)	1.5032(16)
C(5)-H(5)	0.959(14)
C(51)-C(52)	1.3896(17)
C(51)-C(56)	1.3920(17)
C(52)-C(53)	1.3916(18)
C(52)-H(52)	0.953(15)
C(53)-C(54)	1.384(2)
C(53)-H(53)	0.942(16)
C(54)-C(55)	1.385(2)
C(54)-H(54)	0.937(19)
C(55)-C(56)	1.3892(19)
C(55)-H(55)	0.938(18)
C(56)-H(56)	0.951(17)
C(6)-O(3)	1.3399(14)
C(6)-N(1)	1.3760(15)
C(7)-N(2)	1.3232(15)
C(7)-N(1)	1.4116(14)
C(8)-N(2)	1.4487(16)
C(8)-C(9)	1.5049(18)
C(8)-H(8A)	0.960(17)
C(8)-H(8B)	0.957(18)
C(9)-O(4)	1.2004(16)
C(9)-O(5)	1.3342(15)
C(10)-O(5)	1.4631(16)
C(10)-C(11)	1.491(2)
C(10)-H(10A)	0.95(2)
C(10)-H(10B)	0.973(19)
C(11)-H(11A)	0.97(2)
C(11)-H(11B)	0.98(2)
C(11)-H(11C)	1.00(2)
N(2)-H	0.856(19)
O(4)-H	2.310(18)

Table 4. Bond angles [deg] for ***anti*-119**.

C(6)-S(1)-H	78.9(5)
C(2)-C(1)-H(1A)	113.6(11)
C(2)-C(1)-H(1B)	110.6(13)
H(1A)-C(1)-H(1B)	109.0(17)
C(2)-C(1)-H(1C)	111.4(12)
H(1A)-C(1)-H(1C)	100.5(17)
H(1B)-C(1)-H(1C)	111.4(17)
O(1)-C(2)-C(1)	107.37(13)
O(1)-C(2)-H(2A)	108.3(11)
C(1)-C(2)-H(2A)	114.3(11)
O(1)-C(2)-H(2B)	105.9(12)
C(1)-C(2)-H(2B)	110.5(12)
H(2A)-C(2)-H(2B)	110.1(17)
O(2)-C(3)-O(1)	126.03(11)
O(2)-C(3)-C(4)	123.14(11)
O(1)-C(3)-C(4)	110.75(10)
N(1)-C(4)-C(3)	112.26(9)
N(1)-C(4)-C(5)	101.45(9)
C(3)-C(4)-C(5)	112.66(10)
N(1)-C(4)-H(4)	111.2(9)
C(3)-C(4)-H(4)	109.0(9)
C(5)-C(4)-H(4)	110.2(9)
O(3)-C(5)-C(51)	109.71(9)
O(3)-C(5)-C(4)	102.78(9)
C(51)-C(5)-C(4)	116.81(10)
O(3)-C(5)-H(5)	106.5(8)
C(51)-C(5)-H(5)	111.3(8)
C(4)-C(5)-H(5)	109.0(9)
C(52)-C(51)-C(56)	119.50(11)
C(52)-C(51)-C(5)	121.27(11)
C(56)-C(51)-C(5)	119.21(11)
C(51)-C(52)-C(53)	120.04(12)
C(51)-C(52)-H(52)	119.3(9)
C(53)-C(52)-H(52)	120.7(9)
C(54)-C(53)-C(52)	120.24(13)
C(54)-C(53)-H(53)	119.9(10)
C(52)-C(53)-H(53)	119.8(10)
C(53)-C(54)-C(55)	119.90(13)
C(53)-C(54)-H(54)	121.4(11)
C(55)-C(54)-H(54)	118.7(11)
C(54)-C(55)-C(56)	120.08(13)
C(54)-C(55)-H(55)	118.3(11)
C(56)-C(55)-H(55)	121.6(11)
C(55)-C(56)-C(51)	120.22(13)
C(55)-C(56)-H(56)	120.1(10)
C(51)-C(56)-H(56)	119.7(10)
O(3)-C(6)-N(1)	109.48(10)
O(3)-C(6)-S(1)	119.77(9)
N(1)-C(6)-S(1)	130.75(9)
N(2)-C(7)-N(1)	116.87(10)
N(2)-C(7)-S(2)	123.54(9)
N(1)-C(7)-S(2)	119.58(8)
N(2)-C(8)-C(9)	108.52(11)
N(2)-C(8)-H(8A)	111.3(10)
C(9)-C(8)-H(8A)	109.4(10)
N(2)-C(8)-H(8B)	109.7(10)

C(9)-C(8)-H(8B)	108.8(10)
H(8A)-C(8)-H(8B)	109.1(14)
O(4)-C(9)-O(5)	124.82(12)
O(4)-C(9)-C(8)	124.03(12)
O(5)-C(9)-C(8)	111.14(11)
O(5)-C(10)-C(11)	107.93(12)
O(5)-C(10)-H(10A)	107.9(11)
C(11)-C(10)-H(10A)	112.8(12)
O(5)-C(10)-H(10B)	107.7(11)
C(11)-C(10)-H(10B)	110.0(11)
H(10A)-C(10)-H(10B)	110.4(16)
C(10)-C(11)-H(11A)	111.1(13)
C(10)-C(11)-H(11B)	108.8(12)
H(11A)-C(11)-H(11B)	106.1(17)
C(10)-C(11)-H(11C)	110.4(13)
H(11A)-C(11)-H(11C)	111.0(19)
H(11B)-C(11)-H(11C)	109.5(18)
C(6)-N(1)-C(7)	129.01(10)
C(6)-N(1)-C(4)	110.65(9)
C(7)-N(1)-C(4)	119.39(9)
C(7)-N(2)-C(8)	121.74(11)
C(7)-N(2)-H	118.4(12)
C(8)-N(2)-H	119.9(12)
C(3)-O(1)-C(2)	116.57(11)
C(6)-O(3)-C(5)	111.31(9)
C(9)-O(4)-H	82.2(5)
C(9)-O(5)-C(10)	115.00(11)

Appendix A

Table 5. Anisotropic displacement parameters ($A^2 \times 10^3$) for ***anti*-119**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
S(1)	28(1)	25(1)	19(1)	6(1)	-4(1)	-6(1)
S(2)	27(1)	26(1)	27(1)	10(1)	-5(1)	-7(1)
C(1)	26(1)	39(1)	62(1)	7(1)	13(1)	8(1)
C(2)	29(1)	50(1)	37(1)	-11(1)	11(1)	7(1)
C(3)	20(1)	23(1)	19(1)	-1(1)	0(1)	-3(1)
C(4)	18(1)	19(1)	17(1)	1(1)	-2(1)	1(1)
C(5)	17(1)	21(1)	19(1)	2(1)	-1(1)	2(1)
C(51)	19(1)	22(1)	19(1)	1(1)	0(1)	-2(1)
C(52)	24(1)	24(1)	24(1)	2(1)	-1(1)	2(1)
C(53)	36(1)	21(1)	28(1)	-1(1)	6(1)	0(1)
C(54)	43(1)	29(1)	20(1)	-4(1)	3(1)	-6(1)
C(55)	35(1)	36(1)	21(1)	1(1)	-7(1)	-1(1)
C(56)	24(1)	27(1)	24(1)	0(1)	-4(1)	3(1)
C(6)	17(1)	20(1)	19(1)	0(1)	3(1)	-1(1)
C(7)	16(1)	18(1)	21(1)	0(1)	1(1)	1(1)
C(8)	26(1)	24(1)	23(1)	2(1)	-5(1)	-7(1)
C(9)	27(1)	26(1)	23(1)	1(1)	-3(1)	-4(1)
C(10)	40(1)	41(1)	24(1)	6(1)	-12(1)	-8(1)
C(11)	38(1)	51(1)	30(1)	2(1)	-12(1)	-10(1)
N(1)	17(1)	18(1)	16(1)	1(1)	-1(1)	0(1)
N(2)	25(1)	22(1)	19(1)	2(1)	-2(1)	-7(1)
O(1)	21(1)	31(1)	23(1)	-1(1)	3(1)	7(1)
O(2)	32(1)	37(1)	18(1)	3(1)	2(1)	-2(1)
O(3)	22(1)	24(1)	18(1)	2(1)	-2(1)	-6(1)
O(4)	52(1)	42(1)	32(1)	14(1)	-13(1)	-21(1)
O(5)	31(1)	31(1)	21(1)	3(1)	-8(1)	-10(1)

Appendix A

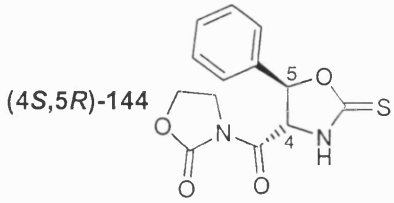
Table 6. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) for ***anti*-119**.

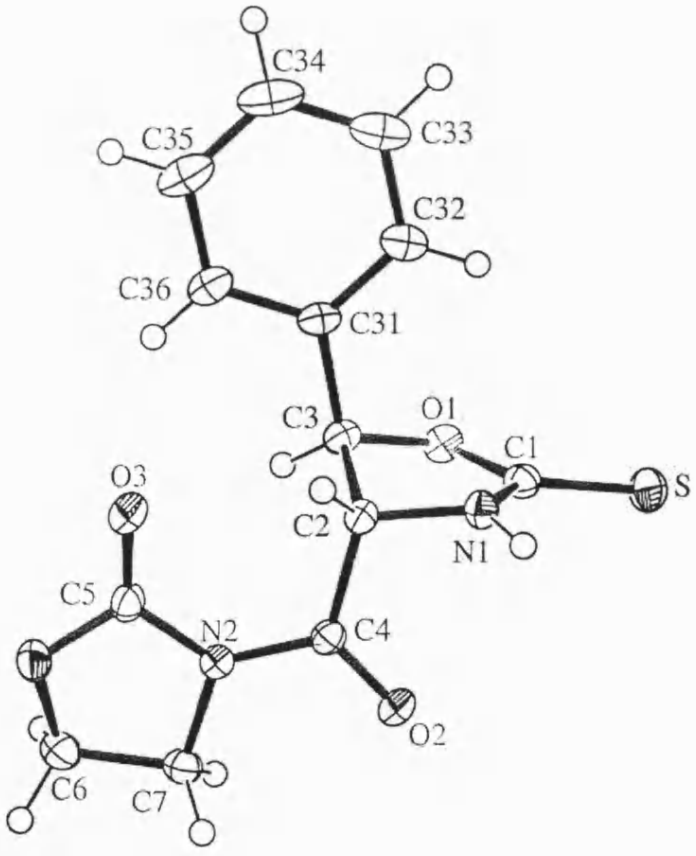
	x	y	z	U(eq)
H(1A)	4818(8)	1350(30)	1940(9)	57(6)
H(1B)	5173(9)	1900(30)	1398(9)	60(6)
H(1C)	5015(8)	3350(30)	1884(9)	50(5)
H(2A)	4385(8)	3750(30)	972(9)	49(5)
H(2B)	4165(9)	1710(30)	1068(9)	58(6)
H(4)	2905(6)	6310(20)	1768(6)	23(4)
H(5)	2230(6)	4290(20)	1994(6)	20(3)
H(52)	3082(7)	440(20)	1652(7)	27(4)
H(53)	2898(7)	-1500(20)	828(7)	29(4)
H(54)	2192(8)	-650(30)	66(8)	47(5)
H(55)	1653(8)	1990(30)	138(8)	45(5)
H(56)	1810(7)	3930(20)	972(7)	32(4)
H(8A)	4785(7)	7750(20)	3170(7)	32(4)
H(8B)	4302(7)	8870(30)	3454(7)	34(4)
H(10A)	5568(8)	6360(30)	4783(8)	49(5)
H(10B)	5137(8)	7630(30)	5107(9)	44(5)
H(11A)	6191(9)	8970(30)	4705(10)	68(7)
H(11B)	6120(9)	8530(30)	5362(9)	56(6)
H(11C)	5741(10)	10210(30)	5049(10)	69(7)
H	3921(8)	5480(30)	3417(8)	43(5)

Appendix B

3-((4*S*,5*R*)-5-phenyl-2-thioxo-oxazolidine-4-carbonyl)-oxazolidin-2-one

(4*S*,5*R*)-144





Appendix B

Table 1. Crystal data and structure refinement for **(4*S*,5*R*)-144**.

Identification code	h03mcw1
Empirical formula	C13 H12 N2 O4 S
Formula weight	292.31
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system	orthorhombic
Space group	P 2_1 2_1 2_1
Unit cell dimensions	a = 7.36300(10) A alpha = 90 deg.
	b = 7.46000(10) A beta = 90 deg.
	c = 23.4670(3) A gamma = 90 deg.
Volume	1288.99(3) A^3
Z, Calculated density	4, 1.506 Mg/m^3
Absorption coefficient	0.266 mm^-1
F(000)	608
Crystal size	0.50 x 0.28 x 0.13 mm
Colour, shape	colourless plate
Theta range for data collection	3.77 to 34.96 deg.
Limiting indices	-11<=h<=11, -12<=k<=12, -37<=l<=37
Reflections collected / unique	34996 / 5623 [R(int) = 0.0445]
Completeness to theta = 34.96	99.4 %
Max. and min. transmission	0.9662 and 0.8784
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5623 / 0 / 185
Goodness-of-fit on F^2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0300, wR2 = 0.0672
R indices (all data)	R1 = 0.0386, wR2 = 0.0703
Absolute structure parameter	0.01(4)
Largest diff. peak and hole	0.238 and -0.223 e.A^-3

Appendix B

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **(4*S*,5*R*)-144**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S	9378(1)	11434(1)	7997(1)	28(1)
O(1)	8743(1)	8012(1)	8168(1)	22(1)
O(2)	13473(1)	7554(1)	8087(1)	24(1)
O(3)	11741(1)	3701(1)	9243(1)	27(1)
O(4)	13576(1)	1945(1)	8721(1)	26(1)
N(1)	10888(1)	9079(1)	8727(1)	20(1)
N(2)	13145(1)	4735(1)	8416(1)	20(1)
C(1)	9704(1)	9476(1)	8312(1)	20(1)
C(2)	11101(1)	7157(1)	8783(1)	18(1)
C(3)	9234(1)	6533(1)	8547(1)	20(1)
C(31)	7780(1)	6294(1)	8995(1)	22(1)
C(32)	6660(1)	7704(2)	9164(1)	27(1)
C(33)	5357(2)	7435(2)	9590(1)	35(1)
C(34)	5174(1)	5768(2)	9842(1)	37(1)
C(35)	6276(2)	4359(2)	9675(1)	36(1)
C(36)	7578(1)	4612(2)	9250(1)	28(1)
C(4)	12684(1)	6536(1)	8405(1)	18(1)
C(5)	12701(1)	3496(1)	8835(1)	22(1)
C(6)	14382(2)	2015(1)	8151(1)	31(1)
C(7)	14446(1)	4003(1)	8005(1)	24(1)

Appendix B

Table 3. Bond lengths [Å] for **(4*S*,5*R*)-144**.

S-C(1)	1.6549(9)
O(1)-C(1)	1.3442(11)
O(1)-C(3)	1.4631(11)
O(2)-C(4)	1.2128(11)
O(3)-C(5)	1.1989(11)
O(4)-C(5)	1.3511(11)
O(4)-C(6)	1.4634(13)
N(1)-C(1)	1.3408(11)
N(1)-C(2)	1.4483(11)
N(2)-C(4)	1.3861(12)
N(2)-C(5)	1.3886(12)
N(2)-C(7)	1.4651(12)
C(2)-C(4)	1.5367(12)
C(2)-C(3)	1.5537(12)
C(3)-C(31)	1.5102(12)
C(31)-C(32)	1.3940(14)
C(31)-C(36)	1.3984(14)
C(32)-C(33)	1.4000(15)
C(33)-C(34)	1.3832(19)
C(34)-C(35)	1.3843(18)
C(35)-C(36)	1.3962(15)
C(6)-C(7)	1.5224(14)

Appendix B

Table 4. Bond angles [deg] for **(4*S*,5*R*)-144**.

C(1)-O(1)-C(3)	109.26(6)
C(5)-O(4)-C(6)	110.14(7)
C(1)-N(1)-C(2)	110.82(7)
C(4)-N(2)-C(5)	126.94(8)
C(4)-N(2)-C(7)	120.61(7)
C(5)-N(2)-C(7)	111.83(7)
N(1)-C(1)-O(1)	110.20(8)
N(1)-C(1)-S	127.91(7)
O(1)-C(1)-S	121.89(6)
N(1)-C(2)-C(4)	109.13(7)
N(1)-C(2)-C(3)	99.69(7)
C(4)-C(2)-C(3)	112.01(7)
O(1)-C(3)-C(31)	109.67(7)
O(1)-C(3)-C(2)	102.10(7)
C(31)-C(3)-C(2)	114.52(7)
C(32)-C(31)-C(36)	119.49(9)
C(32)-C(31)-C(3)	121.89(9)
C(36)-C(31)-C(3)	118.62(9)
C(31)-C(32)-C(33)	120.02(11)
C(34)-C(33)-C(32)	120.07(11)
C(33)-C(34)-C(35)	120.28(9)
C(34)-C(35)-C(36)	120.14(11)
C(35)-C(36)-C(31)	120.00(10)
O(2)-C(4)-N(2)	120.09(8)
O(2)-C(4)-C(2)	122.03(8)
N(2)-C(4)-C(2)	117.82(7)
O(3)-C(5)-O(4)	123.27(9)
O(3)-C(5)-N(2)	128.22(9)
O(4)-C(5)-N(2)	108.49(7)
O(4)-C(6)-C(7)	104.66(8)
N(2)-C(7)-C(6)	101.23(7)

Appendix B

Table 5. Anisotropic displacement parameters ($A^2 \times 10^3$) for **(4*S*,5*R*)-144**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$.

	U11	U22	U33	U23	U13	U12
S	29(1)	26(1)	30(1)	8(1)	-2(1)	4(1)
O(1)	22(1)	26(1)	19(1)	1(1)	-2(1)	-3(1)
O(2)	24(1)	23(1)	25(1)	4(1)	4(1)	-4(1)
O(3)	29(1)	24(1)	26(1)	6(1)	5(1)	-2(1)
O(4)	24(1)	18(1)	37(1)	2(1)	0(1)	0(1)
N(1)	21(1)	17(1)	21(1)	0(1)	-2(1)	-1(1)
N(2)	20(1)	18(1)	23(1)	1(1)	3(1)	0(1)
C(1)	20(1)	23(1)	18(1)	1(1)	2(1)	1(1)
C(2)	19(1)	17(1)	18(1)	1(1)	1(1)	-2(1)
C(3)	19(1)	21(1)	19(1)	-1(1)	1(1)	-3(1)
C(31)	18(1)	28(1)	19(1)	-3(1)	2(1)	-4(1)
C(32)	22(1)	35(1)	26(1)	-5(1)	2(1)	0(1)
C(33)	23(1)	55(1)	28(1)	-13(1)	4(1)	1(1)
C(34)	24(1)	67(1)	21(1)	-5(1)	4(1)	-11(1)
C(35)	30(1)	51(1)	26(1)	8(1)	2(1)	-12(1)
C(36)	24(1)	32(1)	29(1)	4(1)	3(1)	-6(1)
C(4)	18(1)	18(1)	18(1)	0(1)	-1(1)	-2(1)
C(5)	20(1)	18(1)	27(1)	3(1)	-2(1)	-2(1)
C(6)	26(1)	23(1)	43(1)	-3(1)	8(1)	2(1)
C(7)	20(1)	24(1)	27(1)	-2(1)	5(1)	1(1)

Appendix B

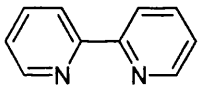
Table 6. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) for **(4*S*,5*R*)-144**.

	x	y	z	U(eq)
H	11700(19)	9851(19)	8827(6)	31(3)
H(2)	11276	6790	9190	22
H(3)	9382	5402	8323	24
H(32)	6782	8848	8990	33
H(33)	4597	8397	9706	42
H(34)	4289	5590	10131	44
H(35)	6146	3218	9850	43
H(36)	8326	3641	9134	34
H(6A)	13626	1352	7873	37
H(6B)	15618	1494	8153	37
H(7A)	15676	4506	8063	29
H(7B)	14054	4225	7608	29

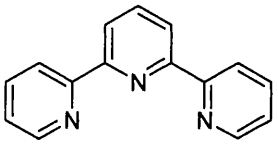
Appendix C

Supply of ligands

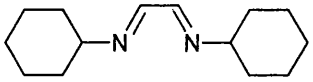
Bipyridine: purchased from Aldrich



Phenanthroline: purchased from Aldrich

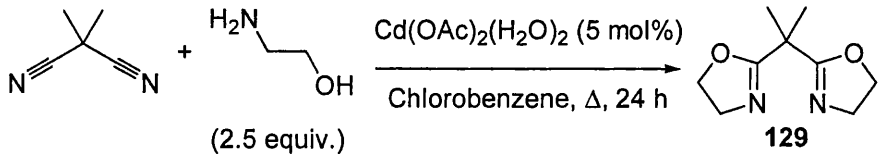


N,N'-Dicyclohexylethanediimine **120**: provided by Chris Chapman



120

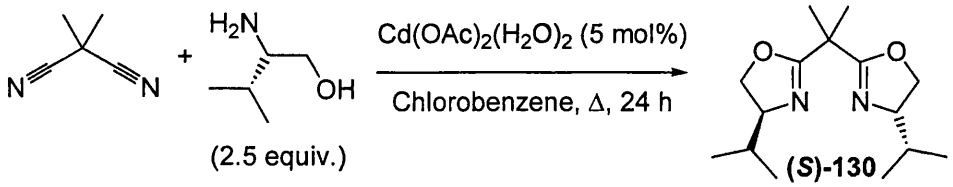
2,2'-Isopropylidenebis-(2-oxazoline) **129**:[120]



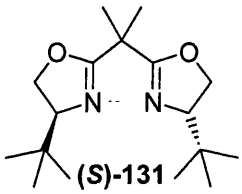
129

Appendix C

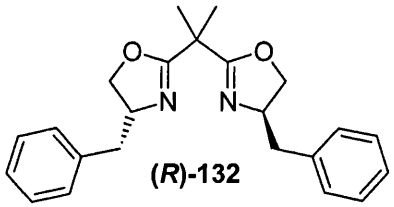
2,2-Bis-[(4'*S*)-4'-*iso*-propyloxazolin-2'-yl]-propane (*S*)-**130**:[158]



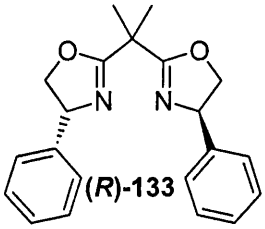
2,2-Bis-[(4'*S*)-4'-*tert*-butyloxazolin-2'-yl]-propane (*S*)-**131**: purchased from Aldrich



2,2-Bis-[(4'*R*)-4'-benzyloxazolin-2'-yl]-propane (*R*)-**132**: purchased from Aldrich

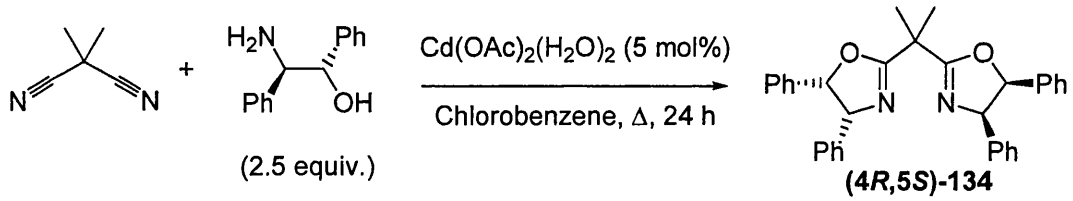


2,2-Bis-[(4'*R*)-4'-phenyloxazolin-2'-yl]-propane (*S*)-**133**: purchased from Aldrich

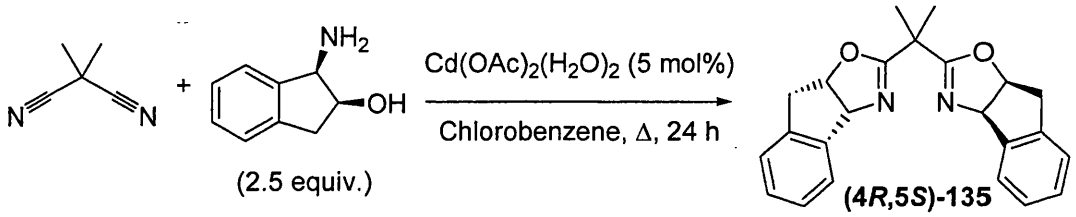


Appendix C

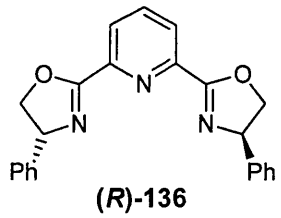
2,2-Bis-[(4'*R*,5'*S*)-4',5'-diphenyloxazolin-2'-yl]-propane (4*R*,5*S*)-**134**:[157]



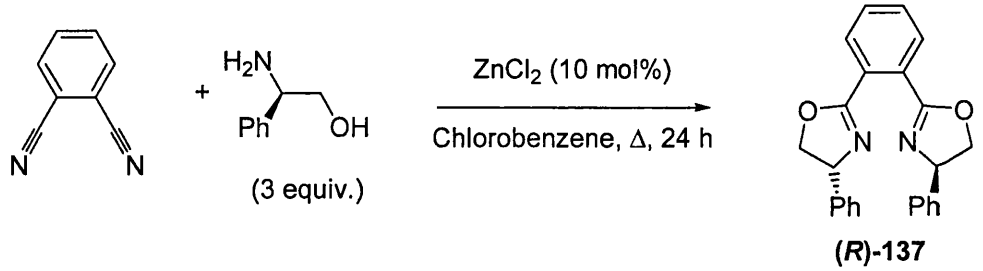
{3a*S*-[2(3'a*R**,8'a*S**),3aα,8aα]}-2,2'-(1-Methylethylidene)-bis-{3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole}(4*R*,5*S*)-**135**:[160]



2,6-Bis-[(4'*S*)-4'-phenyloxazolin-2'-yl]-pyridine (*R*)-**136**: purchased from Aldrich

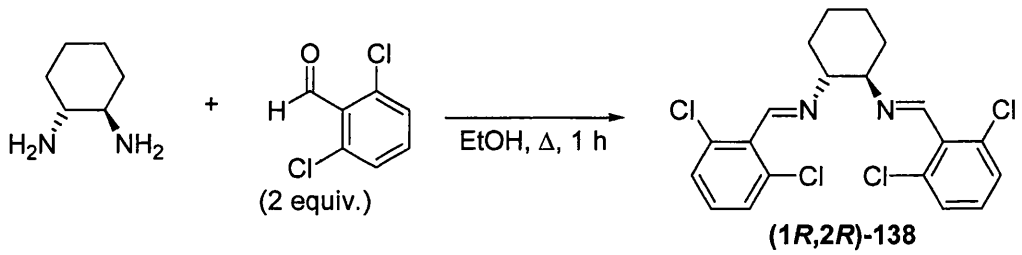


1,2-Bis-[(4'*R*)-4'-phenyloxazolin-2'-yl]-benzene (*R*)-**137**:[124]

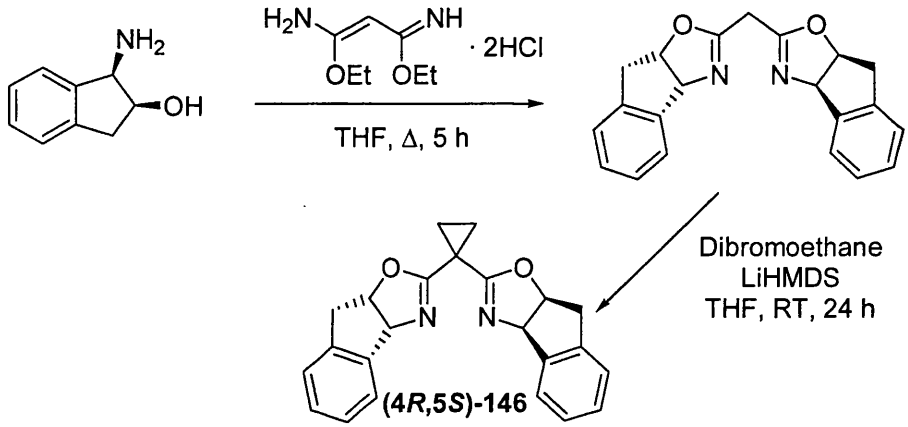


Appendix C

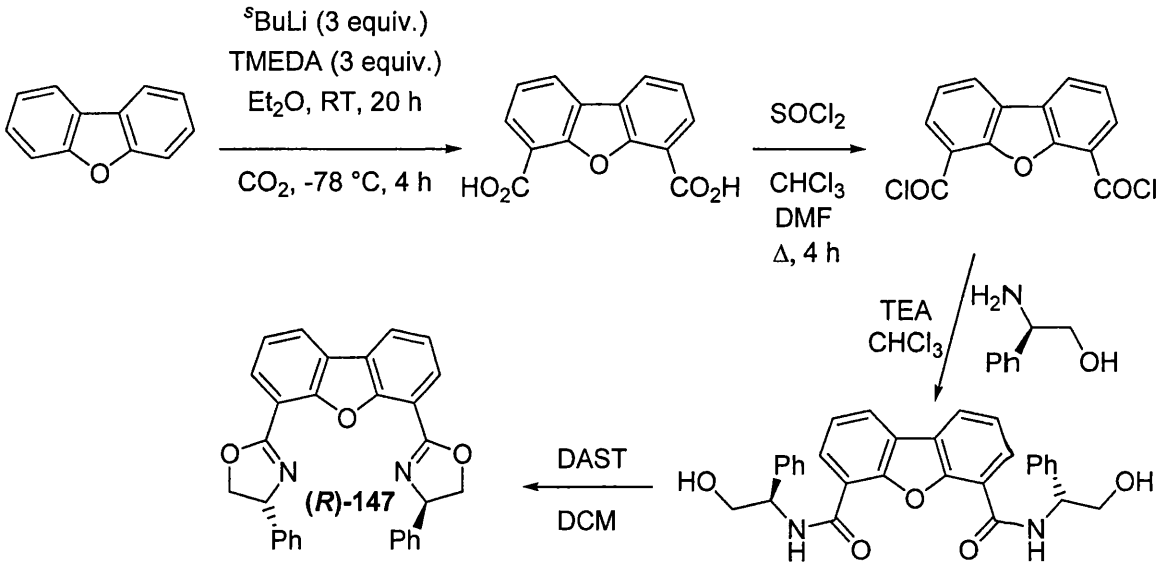
(1*R*,2*R*)-*N*,*N*'-Bis-(2',6'-dichlorobenzylidene)-diaminocyclohexane (1*R*,2*R*)-**138**:[126]



{3a*S*-[2(3'a*R**,8'a*S**),3aα,8aα]}-2,2'-(Cyclopropylidene)-bis-{3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole (4*R*,5*S*)-**146**:[102]

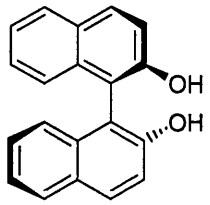


(*R*,*R*)-4,6-Dibenzofurandiyl-2,20-bis-(4-phenyloxazoline) (*R*)-**147**:[159]



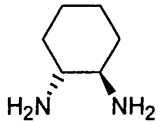
Appendix C

(*R*)-BINOL (*R*)-**148**: purchased from Aldrich



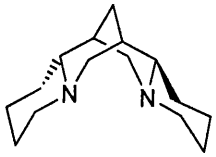
(*R*)-148

(1*R*,2*R*)-Diaminocyclohexane (1*R*,2*R*)-**149**: purchased from Aldrich



(1*R*,2*R*)-149

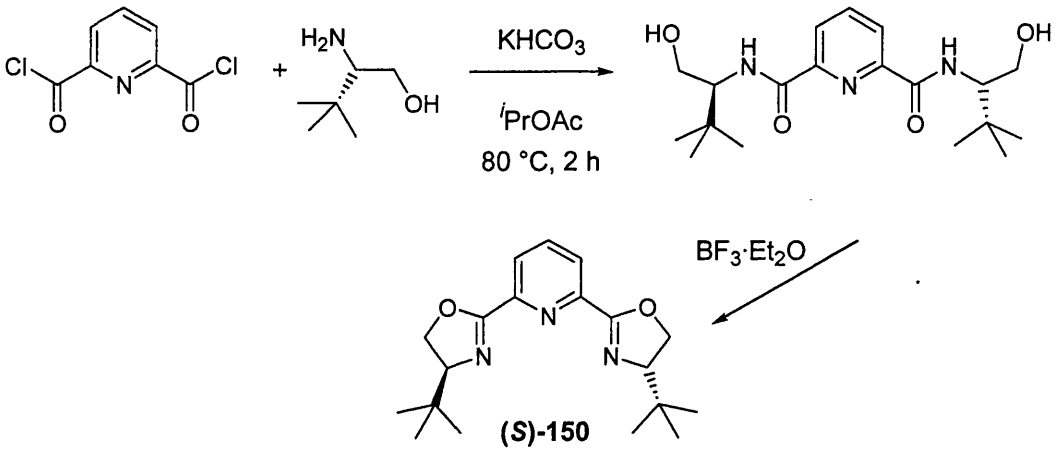
(-)-Sparteine **107**: purchased from Aldrich



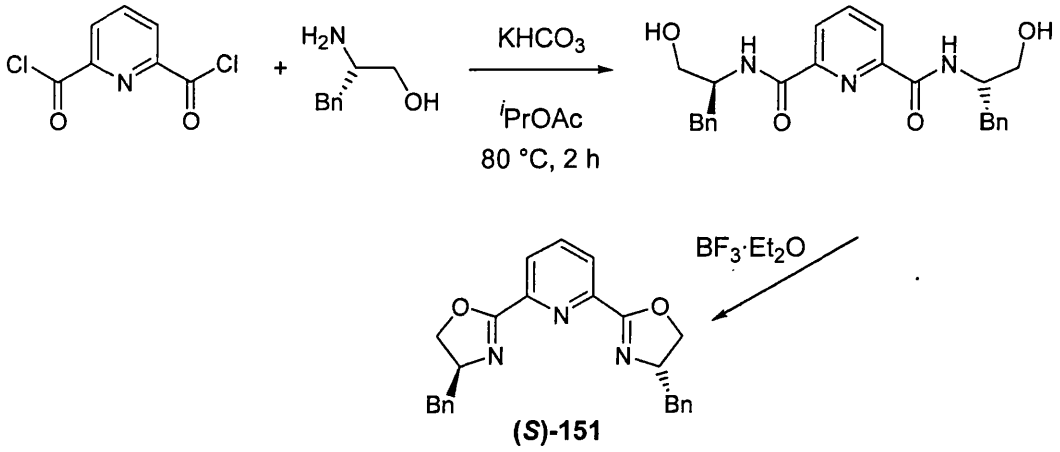
107 (-)-sparteine

Appendix C

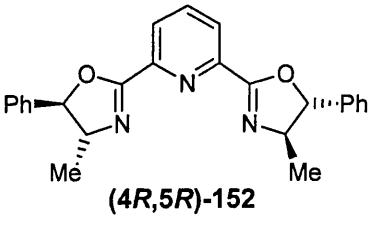
2,6-Bis-[(4'*S*)-4'-*tert*-butyloxazolin-2'-yl]-pyridine (*S*)-**150**:[36]



2,6-Bis-[(4'*S*)-4'-benzyloxazolin-2'-yl]-pyridine (*S*)-**151**:[156]

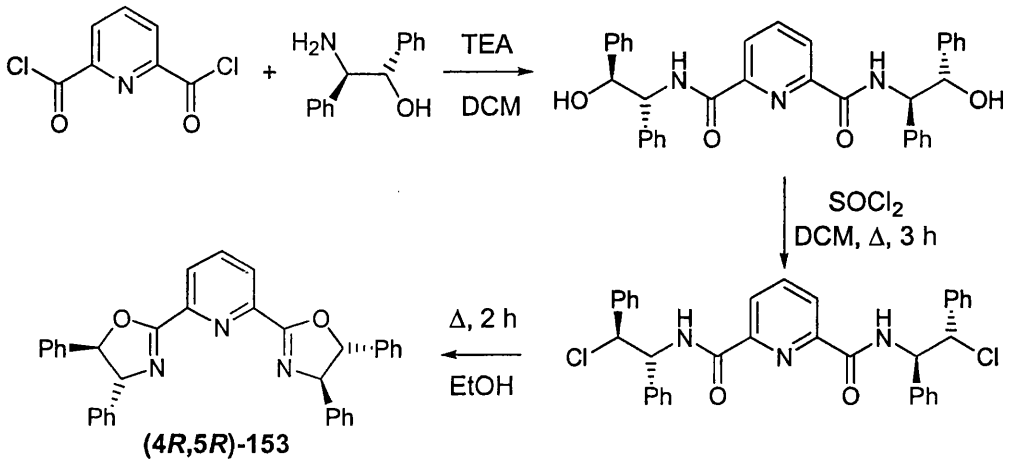


2,6-Bis-[(4'*R*,5'*R*)-4'methyl-5'-phenyloxazolin-2'-yl]-pyridine (4*R*,5*R*)-**152**: purchased from Aldrich

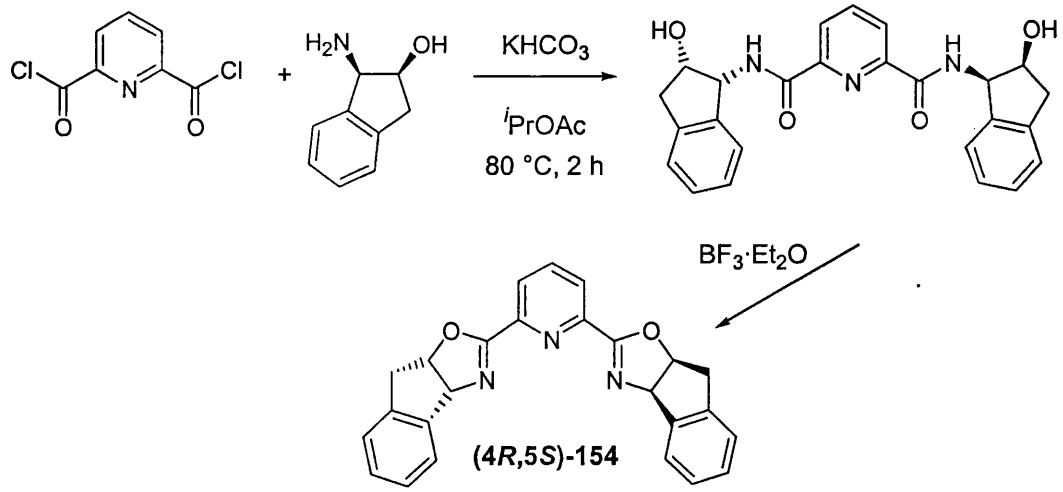


Appendix C

2,6-Bis-[(4'*R*,5'*R*)-4',5'-diphenyloxazolin-2'-yl]-pyridine (4*R*,5*R*)-**153**:[135]



{3a*S*-[2(3'a*R**,8'a*S**),3aα,8aα]}-2,2'-(2,6-Pyridinediyl)-bis-{3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole} (4*R*,5*S*)-**154**:[134]



Appendix D

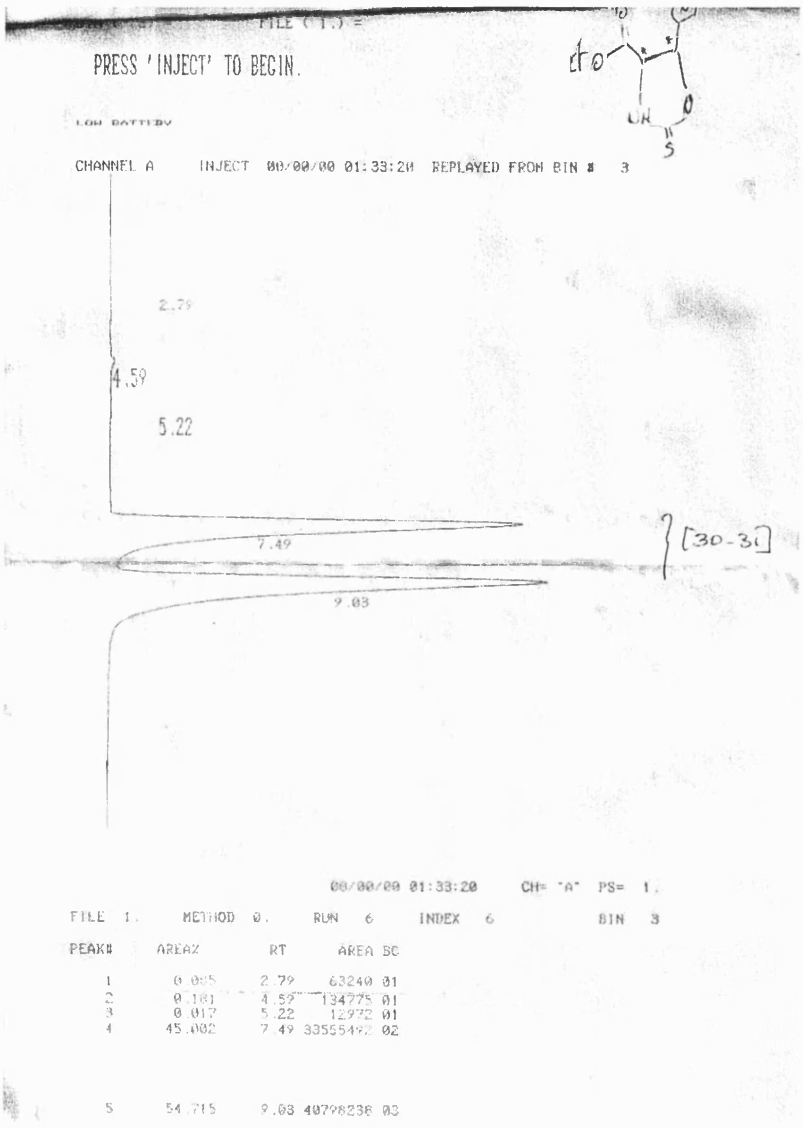
General conditions used to record the following chromatograms:

HPLC was carried out using Thermo Separation Products spectra SERIES P200, using the Chiralcel® OD00CE-IJ033 column. The loading loop was 20 μL. The eluant employed was an isocratic mixture of hexane and IPA (80:20 respectively) at a flow of 1 $mL.min^{-1}$. A TSP spectra SERIES UV100 detector was fitted to the outlet of the column and indicated the absorption at 254 nm, r = 0.0005. Retention times are reported in minutes.

- Chromatogram 1: racemic mixture of *syn*-**118**.
- Chromatogram 2: racemic mixture of *anti*-**118**.
- Chromatogram 3: racemic mixture of *syn*-**145**.
- Chromatogram 4: racemic mixture of *anti*-**145**.
- Chromatogram 5: (4*S*,5*R*)- and *anti*-**145**.
- Chromatogram 6: (4*S*,5*R*)-**145**.

Appendix D

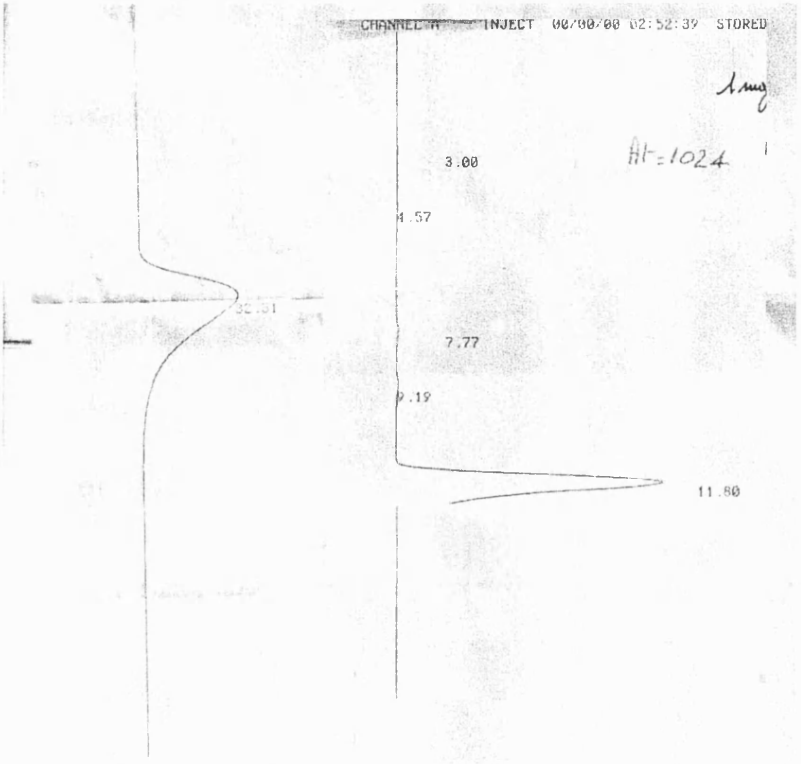
Chromatogram 1: racemic mixture of *syn*-**118**.



Solution of the *syn*-oxazolidinethiones *syn*-**118** in hexane and IPA (70:30 respectively) (20 μL, 1.3 mg.mL^{-1}). Attenuation was 1024. The racemic mixture was obtained following Hoppe's method.[103,104] tr_1 = 7.5 min; tr_2 = 9.0 min.

Appendix D

Chromatogram 2: racemic mixture of *anti*-**118**.



00/00/00 02:52:39 CH= "A" PS= 1.

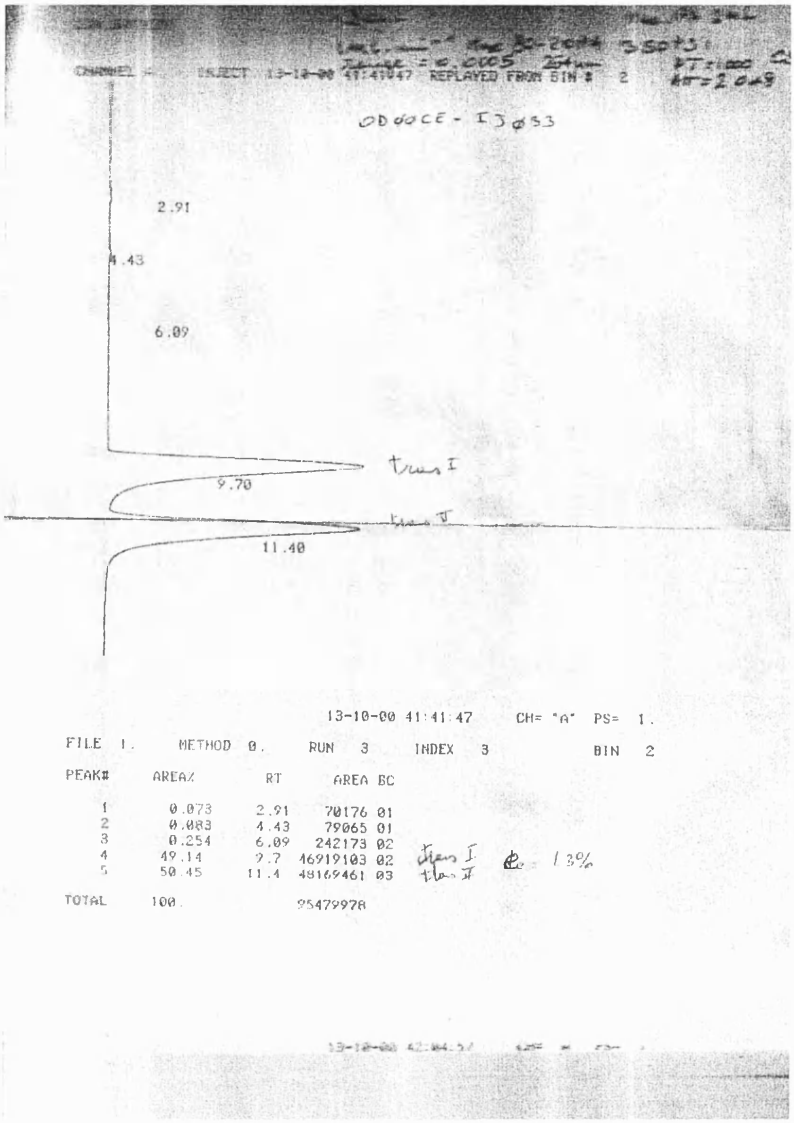
FILE 1. METHOD 0. RUN 7 INDEX 7 BIN 4

PEAK#	AREA%	RT	AREA	BC
1	0.015	3.	9218	01
2	0.051	4.57	31198	01
3	0.259	7.77	158386	01
4	0.277	9.19	169557	01
5	48.459	11.8	29663191	01
6	50.939	32.31	31181149	01
TOTAL	100.		61212699	

Solution of the *anti*-oxazolidinethiones *anti*-**118** in hexane and IPA (70:30 respectively) (20 µL, 1.3 $mg.mL^{-1}$). Attenuation was 1024. The racemic mixture was obtained following Hoppe's method.[103,104] tr_1 = 11.8 min; tr_2 = 32.3 min.

Appendix D

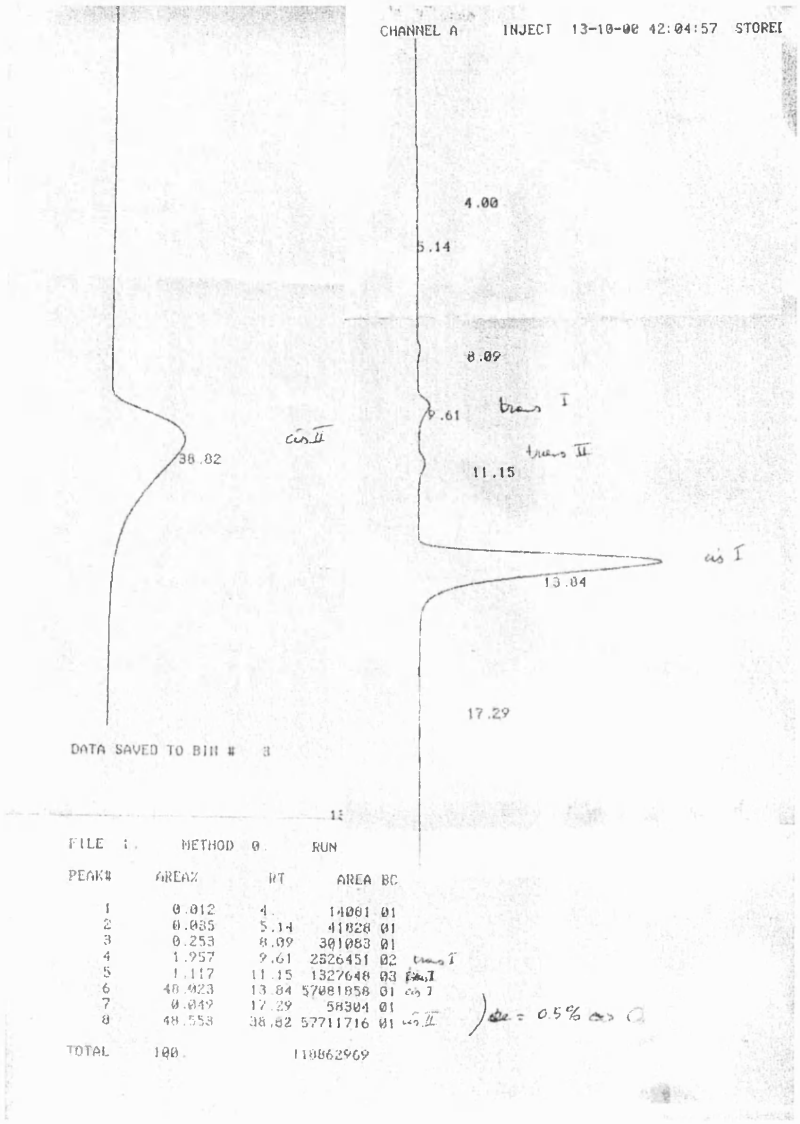
Chromatogram 3: racemic mixture of *syn*-**145**.



Solution of the *syn*-oxazolidinethiones *syn*-**145** in hexane and IPA (50:50) (20 µL, 0.75 $mg.mL^{-1}$). Attenuation was 2048. The racemic mixture was obtained by methanolysis of *syn*-**144**, which was synthesized by reaction of OxNCSAc **116** with benzaldehyde **12** (1.1 equiv.) catalysed by $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%) and TEA (20 mol%) in THF at 0 °C. tr_1 = 9.7 min; tr_2 = 11.4 min.

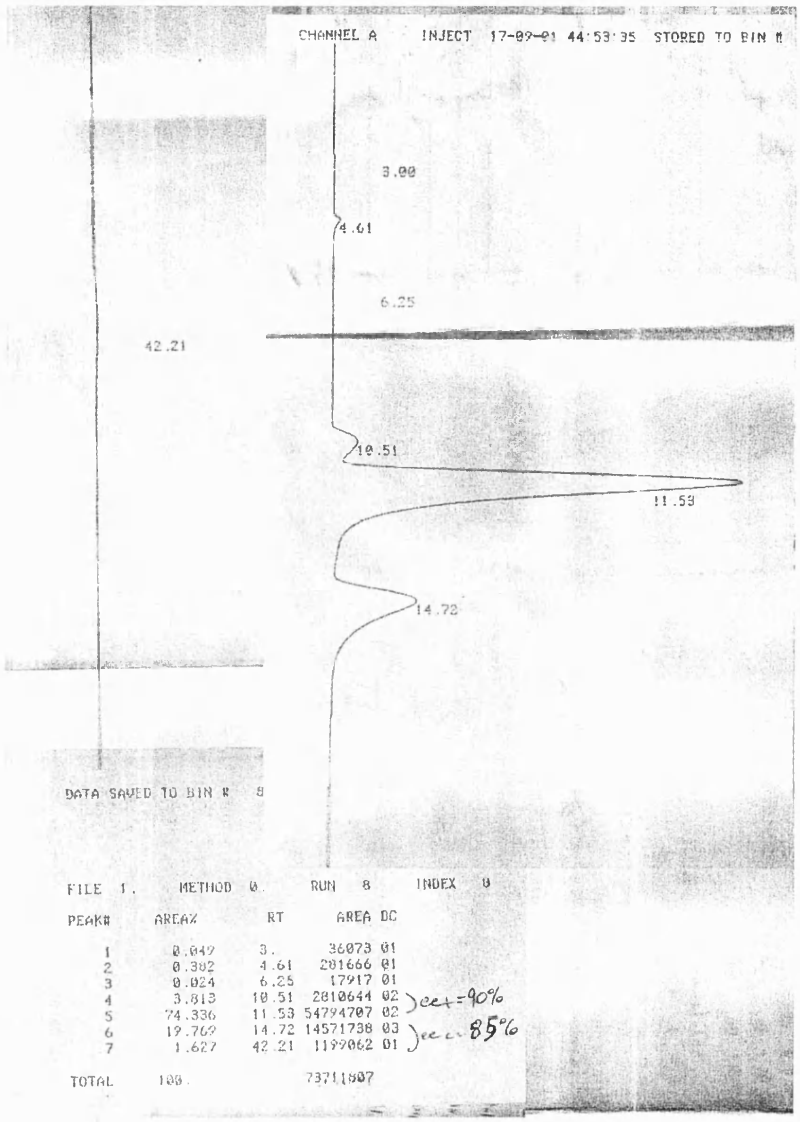
Appendix D

Chromatogram 4: racemic mixture of *anti*-**145**.



Solution of the *anti*-oxazolidinethiones *anti*-**145** in hexane and IPA (50:50) (20 µL, 0.75 $mg.mL^{-1}$). Attenuation was 2048. The racemic mixture was obtained by methanolysis of *anti*-**144**, which was synthesized by reaction of OxNCSAc **116** with benzaldehyde **12** (1.1 equiv.) catalysed by $Mg(ClO_4)_2$ (10 mol%), bipyridine (10 mol%) and TEA (20 mol%) in THF at 0 °C. tr_1 = 13.8 min; tr_2 = 38.8 min.

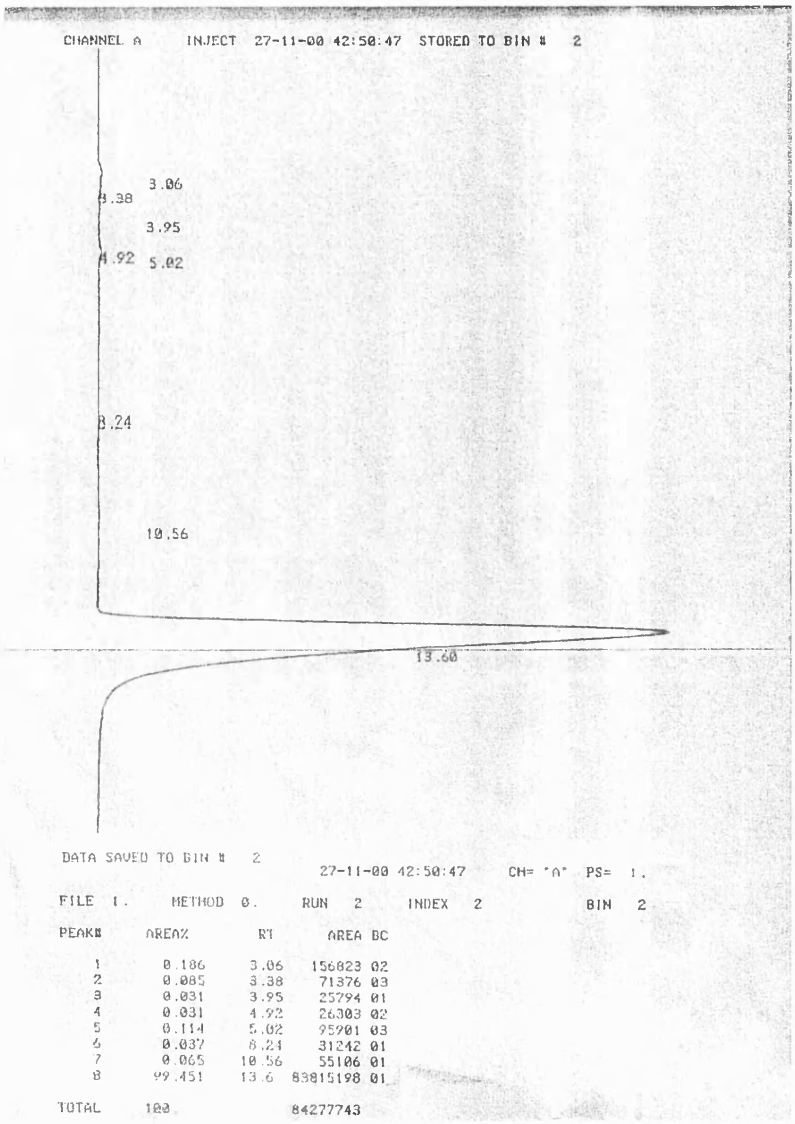
Chromatogram 5: (4*S*,5*R*)- and *anti*-**145**.



Solution of a sample composed of *syn* and *anti*-oxazolidinethiones *syn*- and *anti*-**145** in hexane and IPA (50:50) (20 µL, 0.5 mg.mL^{-1}). Attenuation was 1024. The sample was obtained by methanolysis of a crude of *syn*- and *anti*-**144**, synthesized by reaction of OxNCSAc **116** with benzaldehyde **12** (1.1 equiv.) catalysed by $Mg(ClO_4)_2$ (10 mol%), (*R*)-PhPyBOx (***R*)-136** (11 mol%) and DIPEA (20 mol%) in DCM with 4 Å MS at -78 °C. tr_1 = 10.5 min; tr_2 = 11.5 min; tr_3 = 14.7 min; tr_4 = 42.2 min. Major compound: (4*S*,5*R*)-**145**.

Appendix D

Chromatogram 6: (4*S*,5*R*)-**145**.



Solution of (4*S*,5*R*)-oxazolidinethione (4*S*,5*R*)-**145** in hexane and IPA (50:50) (20 µL, 0.8 mg.mL^{-1}). Attenuation was 1024. The sample was obtained by methanolysis of (4*S*,5*R*)-**144**, which was synthesized by reaction of OxNCSAc **116** with benzaldehyde **12** (1.1 equiv.) catalysed by $Mg(ClO_4)_2$ (10 mol%), (*R*)-PhPyBOx **(*R*)-136** (11 mol%) and DIPEA (20 mol%) in DCM with 4 Å MS at -78 °C, purified by flash chromatography and recrystallised twice from DCM-hexane. tr_1 = 13.6 min.

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